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KERATOSIS FOLLICULARIS (DARIER'S DISEASE)

A VITAMIN A DEFICIENCY DISEASE

SAMUEL M. PECK, M.D.

LOUIS CHARGIN, M.D.

AND

HARRY SOBOTKA, PH.D.

NEW YORK

Many cases of keratosis follicularis have been reported since it was first described, in 1889, by Darier and independently by J. C. White. Darier's original assumption that the disease was of parasitic origin (psorosperm) has been disproved. All textbooks and papers to date state that the cause is unknown and that the condition is extremely refractory to all forms of therapy.

Several years ago (1938) one of us (S. P.) had occasion to study a typical case of Darier's disease in a man aged 25. It occurred to Peck that because the chief pathologic change was dyskeratosis the process might be a vitamin A deficiency. Accordingly, the patient was treated with large doses of vitamin A by mouth. This therapy resulted in a remarkable involution of the cutaneous condition. It was also noted that there was a slow but progressive recurrence when the administration of the vitamin was discontinued.

The assumption that keratosis follicularis represents a vitamin A deficiency could not be verified, however, until a reliable method for the assay of vitamin A in the blood was developed; only then were we able to carry out the studies in the cases reported in this communication.

METHODS

Quantitative estimation of vitamin A in the blood serum was carried out by Dr. Susan Kann according to the method of Carr and Price with a photoelectric colorimeter.[1] The lower normal limit of vitamin A

From the Dermatologic Service and the Laboratories of the Mount Sinai Hospital.

1. Carr, F. H., and Price, E. A.: Colour Reactions Attributed to Vitamin A, Biochem. J. **20**:497, 1926. Dann, W. J., and Evelyn, K. A.: Determination of Vitamin A with Photoelectric Colorimeter, ibid. **32**:1008. 1938. This instrument, known as the photelometer, is made by the Central Scientific Company, Chicago.

figures obtained by this method is variably given at 60 to 90 U. S. P. units per hundred cubic centimeters of blood serum.

Dr. Selig Hecht, of the department of biophysics of Columbia University, studied 2 of our cases (cases 1 and 2 in the table) with his excellent method for measurement of dark adaptation [2] as a gage of vitamin A deficiency in human beings.

REPORT OF CASES

CASE 1.—E. S., a white man aged 25, had had an eruption on the back of the ears, scalp and face for about five years before we saw him. No other member of the family had ever been affected with this condition as far as the patient's father, a physician, could establish.

A general physical examination revealed a rather obese man with stigmas of hypopituitarism and an undescended right testis. The patient presented a typical picture of Darier's disease with single hyperkeratotic papules which in places had become confluent and formed large plaques. These were on the scalp, behind the ears, in the labionasal folds and on the forehead. The axillas were also affected. On the abdomen at about the level of the umbilicus the papules formed large bands of hyperkeratotic tissue. Similarly involved areas were also present in the inguinal region and around the anus.

Laboratory Findings.—The basal metabolic rate was + 13 per cent. A specimen of tissue for biopsy was taken from behind the right ear. The histologic examination showed an acanthotic epidermis, especially at the follicles. These were filled with many densely laminated horny plugs. There was no dyskeratosis in the follicles. Between the follicles were several areas within the horny layer which dipped deep into the epidermis. Below this the epidermis, especially that above the basal cell margin, was separated and showed many *corps ronds.* A moderate inflammatory process was observed in the upper part of the cutis.

Treatment and Course.—The patient was first seen on Aug. 1, 1938. Previously he had received roentgen ray therapy and had applied ointment, with little, if any, improvement. He was on a normal diet. He ate a sufficient amount of such products as butter; so there was no question of his diet being deficient in vitamin A.

Treatment was begun with 50,000 U. S. P. units of vitamin A per day given by mouth. This dose was increased to 65,000 units per day. As improvement became apparent and continued, the amount of vitamin A was increased to 100,000 units per day.

About four months after this treatment had been initiated, the abdominal and facial lesions had improved a great deal, but the lesions behind the ears and in the other cutaneous folds were still to be seen. When the amount of vitamin A was increased to 200,000 U. S. P. units per day the other areas, previously resistant to treatment, also began to improve.

During the course of observation and experimentation the administration of vitamin A was discontinued for various periods, and it was clearly noticeable that manifestations of the disease returned, although very slowly, just as they had disappeared. When the vitamin A was given again in amounts of 200,000 U. S. P. units a day, improvement could again be noticed.

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2. Hecht, S., and Mandelbaum, J.: Dark Adaptation and Experimental Human Vitamin A Deficiency, Am. J. Physiol. **130**:651-664 (Oct.) 1940.

As can be noted from the table, two weeks after the administration of vitamin A had been discontinued the blood was examined, on Aug. 15, 1940. It showed 30 U. S. P. units of vitamin A and 367 micrograms of carotene per hundred cubic centimeters of serum.

The patient was again given 200,000 U. S. P. units of vitamin A per day, and on September 3 his blood was reexamined. It showed 205 units of vitamin A and 327 micrograms of carotene per hundred cubic centimeters of serum. The administration of vitamin A was then discontinued for one week, and a dark adaptation test, performed by Dr. Hecht on September 10, showed normal vision.

Vitamin A and Carotene Studies in Four Cases of Keratosis Follicularis

Name, Age, Sex	Duration	Heredity	Comment	Date of Examination	Vitamin A in Serum, International Units	Carotene in Serum, Micrograms	Dark Adaptation
E. S. 27 M	5 years	None	Had been taking 150,000 to 200,000 units of vitamin A daily for about two years; administration stopped two weeks before blood examination	8/15/40	38	367	.....
			200,000 units of vitamin A per day since last blood examination	9/ 3/40	245	327	.....
			Administration of vitamin A discontinued for one week	9/10/40	..	...	Normal
			200,000 units of vitamin A per day since 9/10/40; administration discontinued for six days before examination of blood	9/30/40	84	355	.....
			Vitamin A still not given	10/15/40	64	215	.....
Car. 47 M	Since childhood	None	Normal diet	9/10/40	48	201	Not done
			Vitamin A given (200,000 units per day)	10/ 7/40	59	150	.....
P. K. 27 F	14 years	None	Normal diet	9/22/40	48	128	1/10 normal
C. N. 26 F	9 years	Fourth generation so affected	Normal diet	11/ 4/40	47	153	Not done

Vitamin A was again given for two weeks, and its administration was then discontinued for six days before the blood was next examined, on September 9. These results showed 84 U. S. P. units of vitamin A and 355 micrograms of carotene per hundred cubic centimeters of serum. Without resumption of administration of vitamin A, the blood was reexamined on October 15. It showed 64 U. S. P. units of vitamin A and 215 micrograms of carotene per hundred cubic centimeters of serum.

These results clearly demonstrated that there was a rapid increase of vitamin A in the serum when large amounts were given by mouth, but with the patient on a normal diet the amount of vitamin A in the circulation gradually decreased.

CASE 2.—D. C., a white man, born in Italy, had had this disease since childhood. He stated the belief that coincidentally with the eruption he began to have gastric distress which sometimes led to vomiting; this has continued. As far as could be elicited from the patient, no other member of the family had ever been affected.

A general physical examination showed nothing abnormal. Examination of the stomach and duodenum by roentgen rays and examination of the gastric contents revealed no evidence of organic lesions. When the patient was first seen, in 1936, he presented widespread involvement of the skin affecting his face and neck and the so-called seborrheic areas of the chest and back. There were also lesions in the axillas and in the groin, as well as on the dorsa of the hands. The primary lesions were millet seed-sized hyperkeratotic papules, many of which showed a central horny plug. In places confluence formed larger plaques. The involved areas also showed hyperpigmentation. Scattered on the legs, especially on the extensor surfaces, were isolated papules, and scattered lesions could be seen throughout the scalp.

On Sept. 10, 1940 practically the same condition existed, but it was more extensive.

Laboratory Findings.—The Wassermann reaction of the blood was negative. A biopsy on Sept. 1, 1936 showed decided hyperkeratosis and acanthosis, especially involving the stratum granulosum in the vicinity of the hair follicles. There were many *corps ronds.* A diagnosis of Darier's disease was made.

Treatment and Course.—The patient received many ointments and other therapy, but with no appreciable effect on the lesions. He was on a normal diet, which apparently had adequate amounts of vitamin A.

On Sept. 10, 1940 the patient was given 200,000 U. S. P. units of vitamin A per day by mouth, with progressive improvement in the eruption up to the last observation, in November. As the lesions underwent involution, areas where the papules had been present were indicated by brownish, pigmented spots. Some of the healed areas almost gave the impression of atrophic macules.

Examination of the blood on Sept. 10, 1940, before the vitamin A therapy was started, showed 48 U. S. P. units of vitamin A and 200 micrograms of carotene per hundred cubic centimeters of serum. Examination on October 7, after vitamin A had been taken since the first examination, showed that the vitamin A level had risen to 59 U. S. P. units, while the carotene amounted to 150 micrograms, per hundred cubic centimeters of serum. The last examination, on October 29, showed that the amount of vitamin A had risen to 65 U. S. P. units (i. e., the lower limit of normal), while the carotene amounted to 190 micrograms, per hundred cubic centimeters of blood serum.

The examinations of the blood showed that this patient required large amounts of vitamin A to cause a very slow increase in the vitamin A content of his serum. This would tend to indicate that probably there was very poor absorption of vitamin A from the gastrointestinal tract.

CASE 3.—P. K., a married white woman, born in the United States, had an eruption which first appeared fourteen years before we saw her. She was the mother of a 7 month old child, who showed no manifestation of the disease. So far as is known, she was the only member of her family so affected. She visited the Mayo Clinic six years before we saw her, and on examination an eruption which had then persisted for about eight years was diagnosed as Darier's disease. This diagnosis was confirmed by histologic examination.

Examination of the patient revealed an obese woman with no evidence of any organic disease. On Sept. 30, 1940 the skin between her breasts showed brownish, keratotic papules which were isolated and also grouped in plaques. The isolated papules were definitely follicular. The markings of the skin were accentuated. Some hair follicles showed plugs but no formation of papules. Identical changes were seen along the spinal column from about the tenth thoracic to the fourth lumbar vertebra. In the folds of the neck similar processes existed, but here they were in the form of plaques. The axillas showed numerous hyperkeratotic papules and plaques. There was a similar eruption in the region of the mons. There were isolated papules on the flexor surface of the left elbow.

Laboratory Findings.—The basal metabolic rate was + 28 per cent. Examination of the blood on Sept. 20, 1940 showed 48 U. S. P. units of vitamin A and 128 micrograms of carotene per hundred cubic centimeters of blood serum. An ocular examination performed by Dr. Hecht showed the dark adaptation to be one-tenth normal.

Treatment and Course.—Local therapy was ineffective. The patient stated that during her pregnancy she took a compound of various vitamins including vitamin A, with some improvement of the lesions. On Oct. 7, 1940, treatment with 200,000 units of vitamin A per day by mouth was instituted. This has been continued to the present. On October 31 examination of the skin showed decided improvement. The lesions on the neck were practically gone and were just indicated by brownish pigmentations, and this was also true of the lesions around the left elbow. The eruption between the breasts and on the back, while still present, showed decided involution. The lesions were less keratotic, less evident and softer to the touch. Many of the lesions had disappeared, showing somewhat pigmented follicular markings. There was a breaking up of the plaques. The lesions were less pigmented and rather yellowish or reddish.

Case 4.—C. N., a white woman aged 26, a patient of Dr. Frank C. Combes, was seen at the dermatologic clinic of Bellevue Hospital on Oct. 21, 1940. She stated that the eruption began nine years previously on the hands and feet. It progressed gradually and became generalized in a few years, the lesions having persisted up to the present. The family history revealed that the patient's great-grandmother, grandmother, mother and 2 uncles had the same condition. The patient had no living brothers or sisters.

Description of the Lesions.—The scalp was covered with thick greasy scales and crusts. On the forehead, sides of the face, neck, chest, hands, back and lower extremities there were firm pinhead-sized to pea-sized grayish or brownish papules, many covered partially by firmly adherent brownish, greasy, horny crusts. Some of the lesions were discrete, while others, especially those on the back and sacral region, showed a tendency to become confluent. The palms and soles showed a waxy keratosis more than ½ inch (1.3 cm.) in thickness.

Treatment.—Nine years before she came to the clinic, the patient had received some roentgen therapy at the Skin and Cancer Unit of the New York Post-Graduate Medical School and Hospital; this was followed by slight but temporary improvement.

Samples of blood studied on Nov. 4, 1940 showed 47 U. S. P. units of vitamin A and 153 micrograms of carotene per hundred cubic centimeters. The patient was told to take 200,000 U. S. P. units of vitamin A by mouth daily.

COMMENT

This is a preliminary report based on observations in 4 cases.

Patients with keratosis follicularis on a normal diet, which apparently contains an adequate amount of vitamin A, are unable to maintain a normal vitamin A level in the blood, owing either to inability to absorb the required quantity of vitamin A from the gastrointestinal tract or to inability to convert the provitamin A (carotene) into vitamin A. This question is now under investigation.

The figures in the table show a normal level of carotene in the blood even when the administration of vitamin A is withdrawn. This seems to indicate an inability to convert the provitamin to vitamin A. One must bear in mind that vitamin A given therapeutically is not in the form of provitamin A.

The rate of restoration to normal blood levels for vitamin A figures varied in the patients. This was especially noticeable in case 2; although 200,000 U. S. P. units a day was administered from Sept. 10, 1940 to October 29, there was a rise from 48 to only 65 U. S. P. units of vitamin A per hundred cubic centimeters when the last examination was made. This would seem to indicate some inherent inability to absorb vitamin A.

In case 1, on the other hand, there was a rapid increase in the vitamin A level of the blood, from 38 to 245 U. S. P. units per hundred cubic centimeters in about three weeks, when the same amount of vitamin A was given as in case 2. This seemed to speak more for an inability of conversion of the provitamin into vitamin A.

Case 1 further illustrates a rather rapid drop from the high vitamin A level in the blood when the large doses by mouth were discontinued.

The normal light adaptation in case 1 may be explained by the fact that the changes which take place in the eye, as in the skin, occur rather slowly. Sufficient reserve had been built up during the long period when vitamin A had been given prior to examination so that deprivation of vitamin A for one week produced no effect on the eye, although the decrease in the intake was already mirrored in the reduction of vitamin A in the blood serum. This explanation also applies to the cutaneous changes. Improvement or recurrence required a rather long period of ingestion or deprivation of vitamin A before changes became apparent. In case 3, Mrs. K., who at the time of examination showed only 49 U. S. P. units of vitamin A per hundred cubic centimeters of blood previous to vitamin A therapy, had at the same time a light adaptation which was one-tenth that of a normal person.

The only case in our series in which there was a hereditary history was case 4. It will be interesting to see whether the hereditary type

of Darier's disease will be parallel in its course to the condition in other cases. It may be possible, by a study such as this, to differentiate the various types of this disease.

SUMMARY

Vitamin A studies in 4 cases of keratosis follicularis (Darier's disease) are reported.

In all 4 cases the patients while on a normal vitamin A–containing diet showed a decided decrease in the vitamin A content of the blood serum. The carotene content of the blood was within normal limits.

In 2 cases good correlation was obtained between the result of a dark adaptation test and the vitamin A deficiency, as evidenced by the findings in the serum.

A dose of 200,000 U. S. P. units of vitamin A was given by mouth daily to 3 patients and caused a gradual disappearance of the eruption. At the same time there was a gradual restoration of the vitamin A content of the blood serum to normal levels.

One is tempted to suggest that in this disease one is dealing with a physiologic nevus with a hereditary weakness in vitamin A absorption or in conversion of provitamin A to vitamin A. This reflects itself in the skin as dyskeratosis.

DIETARY TREATMENT OF SCALY DESQUAMATIVE DERMATOSES OF THE SEBORRHEIC TYPE

I. EXPERIMENTAL FOUNDATION

PAUL GYÖRGY, M.D.
CLEVELAND

Notwithstanding several attempts [1] in the past to establish a causal relation between diet and the condition of the skin, it is surprising that the possible role of accessory food factors of vitamin-like character has been discussed only to a limited extent in the clinical study of dermatoses.[2] It is equally apparent that the approach to experimental dermatologic research on a nutritional basis has not yet received proper consideration. Of the better known relations between dietary deficiencies and pathologic manifestations of the skin in human beings, those occurring in pellagra [3] should be mentioned first. More recently the syndrome of deficiency of vitamin A with its cutaneous lesions has been the subject of study and is now well recognized.[4]

In so far as an experimental basis for clinical observations is concerned, the existence of analogies has been generally ignored between cutaneous manifestations in man and in animals, such as those which have been uncovered by the systematic study of the vitamin G (B_2) complex and of the so-called egg white injury due to vitamin H [5] (biotin). This neglect is due, probably, to the fact that the cutaneous manifestations encountered in animals, mainly in rats suffering from deficiency of the vitamin G (B_2) complex or its various components and in rats with egg white injury, have been described and are still often classified as

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From the Babies and Childrens Hospital and from the Department of Pediatrics, Western Reserve University School of Medicine.

1. Czerny, A.: Die exsudative Diathese, Jahrb. f. Kinderh. **61**:199, 1905; Zur Kenntnis der exsudativen Diathese, Monatschr. f. Kinderh. **4**:1, 1905.

2. Goodman, H.: Dermatologic Symptoms of Vitamin Deficiencies, Arch. Dermat. & Syph. **38**:389 (Sept.) 1938. See bibliography.

3. McCollum, E. V.; Orent-Keiles, E., and Day, H. G.: The Newer Knowledge of Nutrition, ed. 5, New York, The Macmillan Company, 1939, p. 500.

4. Youmans, J. B., and Corlette, M. B.: Specific Dermatoses Due to Vitamin A Deficiency, Am. J. M. Sc. **195**:644 (May) 1938.

5. György, P., in von Pfaundler, M., and Schlossmann, A.: Handbuch der Kinderheilkunde, ed. 4, Berlin, F. C. W. Vogel, 1935, vol. 10, p. 45.

pellagra-like.[6] Pellagra is a disease which, despite its medical, social and economic importance in some areas, such as the cotton districts of the United States, has aroused only limited interest from a dermatologic point of view. Therefore, the possibility that it might be experimentally produced in animals has been not sufficiently stimulating and the application of the results not broad enough for purposes of general dermatologic research.

The object of this paper and a subsequent one is twofold: (1) to point out the analogies between experimentally produced nutritional dermatoses in rats and the scaly desquamative cutaneous lesions of the seborrheic type in man and (2) to produce some evidence to support the practical clinical application of this fact to the treatment of dermatoses in man.

ANALOGY OF SEBORRHEIC CUTANEOUS LESIONS IN MAN TO EGG WHITE INJURY IN RATS

The initial suggestion as to the more common practical clinical significance of experimentally produced dietary manifestations of the skin has been gained from casual observations of rats fed a diet rich in egg white (Chinese commercial egg white),[7] similar to studies made in the past by Boas [6b] and others.[7a] In contrast to pellagra, the disease thus produced is not predominantly peripheral dermatitis but bears the characteristics of seborrheic desquamative dermatitis, similar in gross appearance to the syndrome in infants termed by Moro [8] seborrheid dermatitis, which is more or less equivalent to the seborrheic eczema of Unna in adults. Instead of the term "seborrheid," used by Moro, "seborrheic" has been accepted throughout this paper to describe these qualitatively identical dermatoses in infants and in adults.

The possibility that egg white injury in rats might be related to seborrheic desquamative dermatitis in man furnished the stimulus for a closer examination of its manifestations and pathogenesis, as well as for

6. (*a*) Goldberger, J., and Lillie, R. D.: A Note on an Experimental Pellagra-like Condition in the Albino Rat, Pub. Health Rep. **41**:1025 (May 28) 1926. (*b*) Boas, M. A.: The Effect of Desiccation upon the Nutritive Properties of Egg-White, Biochem. J. **21**:712, 1927. (*c*) Parsons, H. T., and Kelly, E.: The Effect of Heating Egg White on Certain Characteristic Pellagra-Like Manifestations Produced in Rats by Dietary Use, Am. J. Physiol. **104**:150 (April) 1933.

7. György, P.: Rachitis und andere Avitaminosen, Ztschr. f. ärztl. Fortbild. **28**:377 and 417, 1931; footnote 5.

7a. Friedberger, E., and Seidenberg, S.: Weitere Besuche über einseitige Ernährung mit Eiern, Deutsche med. Wchnschr. **53**:1507, 1927. Stenqvist.[39]

8. Moro, E.: Ekzema infantum und Dermatitis seborrhoides, Berlin, Julius Springer, 1932, p. 4.

the chemical study of the curative factor, vitamin H [9] (biotin). Experiments have been carried out which involved about 7,000 rats.

The initial symptom of a progressive disturbance of the skin in rats given a diet rich in raw or commercial egg white consists of dermatitis which is at first confined to the groin and the genitalia and to the neck and around the mouth, in almost complete analogy to intertrigo in infants, the first manifestation of seborrheic dermatitis. In the later stage of the disease in rats brown, adherent scales of varying size and thickness, together with progressive alopecia, become apparent in and around the inflamed areas. As a rule, neither the dermatitis nor the alopecia in these rats has well defined borders. Of particular interest to pediatricians are the small, thin, almost pointlike but also confluent, brown pigmented scales, usually confined to the back and not accompanied by severe dermatitis or alopecia, although both may be present simultaneously with the intertrigo. The symptom of brown pigmentation has also been observed in rats by Parsons [10] but has not been compared with the similar symptom of beginning "cradle cap" as a manifestation of seborrheic dermatitis in infants. The pigmentation is caused by desquamating, hyperkeratotic, adherent epithelial cells which have a high fat (cholesterol) content.[11]

In exceptional cases the disease may involve the skin of the whole body of the rat and may resemble the typical exfoliative dermatitis seen in adults or Leiner's disease (erythroderma desquamativum), its counterpart in infants. The epidermis of the rat is shed in large or small thin scales, which, on account of their rapid and continuous production,

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9. (*a*) György, P.: Attempts to Isolate the Anti-Egg-Injury Factor (Vitamin H), J. Biol. Chem. **119**:xliii (June) 1937; (*b*) The Curative Factor (Vitamin H) for Egg White Injury, with Particular Reference to Its Presence in Different Foodstuffs and in Yeast, ibid. **131**:733 (Dec.) 1939. (*c*) György, P.; Kuhn, R., and Lederer, E.: Attempts to Isolate the Factor (Vitamin H) Curative of Egg White Injury, ibid. **131**:745 (Dec.) 1939. (*d*) Birch, T. W., and György, P.: Physicochemical Properties of the Factor (Vitamin H) Curative of Egg White Injury, ibid. **131**:761 (Dec.) 1939. (*e*) György, P., and Rose, C. S.: Comparative Activity of Vitamin H Curative of Egg-White Injury Administered Orally and Parenterally to Rats, Proc. Soc. Exper. Biol. & Med. **43**:73 (Jan.) 1940. (*f*) György, P.; Melville, D. B.; Burk, D., and du Vigneaud, V.: The Possible Identity of Vitamin H with Biotin and Coenzyme R, Science **91**:243 (March 8) 1940. (*g*) du Vigneaud, V.; Melville, D. B.; György, P., and Rose, C. S.: On the Identity of Vitamin H with Biotin, ibid. **92**:62 (July 19) 1940. (*h*) György.[7] (*i*) György, P.; Rose, C. S.; Hofmann, K.; Melville, D. B., and du Vigneaud, V.: A Further Note on the Identity of Vitamin H with Biotin, ibid. **92**:609 (Dec. 27) 1940.

10. Parsons, H. T.: The Physiological Effects of Diets Rich in Egg White, J. Biol. Chem. **90**:351 (Jan.) 1931.

11. Moncorps: Zur Frage des Vitamin H, Dermat. Wchnschr. **103**:1230 (Sept. 5) 1936.

become colorless and devoid of fat, the brown color and the high fat content being confined to the first, long adherent scales. Because of blepharitis, the eyelids often stick together and are covered with yellow scales. Generalized alopecia and pruritus are often observed. In black or piebald rats depigmentation of the fur becomes noticeable, and the black hair turns brownish or even gray. Excoriations heal slowly. Cutaneous abscesses are rare, and when present they are ecthyma-like. Mild, sublingual ulcers are fairly common. Spastic gait, due probably to hypertonicity of the striated muscles, particularly of the hindlegs, is a characteristic symptom of egg white injury in the advanced stage.

Administration of the specific curative factor in proper doses, even without any change in the experimental basal diet, restores normal conditions in from two to four weeks. The best and most potent sources of biotin are liver, kidney, yeast and, to a limited extent, cow's milk. Beef muscle is not only devoid of biotin but seems to have an activating effect on the manifestations of egg white injury.[9b] The minimum curative dose for the experimental conditions chosen [12] is represented by 0.5 Gm. of fresh beef liver, 1 Gm. of fresh beef kidney, 0.3 to 0.6 Gm. of dry yeast or about 10 cc. of cow's milk. By means of systematic research, water-soluble concentrates have been prepared [13] in which the curative "rat day dose" orally administered corresponded to from 0.25 to 0.5 mg. of organic solids and, in the case of specially purified concentrates, to 0.025 mg. One third to one fifth of this dose proved equally efficacious in parenteral administration.

Recent experiments [14] have definitely established the identity of vitamin H, the curative factor for egg white injury, with biotin and coenzyme R. Biotin and coenzyme R are extremely potent factors for the growth of yeast and other bacteria.[15] The rat day dose of biotin is one of the lowest known among vitamin-like substances; it is 0.05 microgram of biotin methyl ester.[9i]

ANALOGY OF SEBORRHEIC CUTANEOUS LESIONS IN MAN TO DEFICIENCY DISEASES CAUSED BY PYRIDOXINE (VITAMIN B_6) AND RELATED FACTORS IN RATS

In contrast to experimental egg white injury in rats, the disease due to deficiency of pyridoxine in rats is characterized by symmetric lesions of the skin which affect mainly the peripheral parts of the body, such as

12. György (footnote 9 *a* and *b*).

13. György and others (footnote 9 *a*, *b*, *c* and *d*).

14. György, Melville, Burk and du Vigneaud.[9f] du Vigneaud, Melville, György and Rose.[9g] György, Rose, Hofmann, Melville and du Vigneaud.[9i]

15. Allison, F. E.; Hoover, S. R., and Burk, D.: A Respiration Coenzyme, Science **78**:217 (Sept. 8) 1933. Kögl, F., and Tönnis, B.: Ueber das Bios-Problem. Darstellung von krystallisiertem Biotin aus Eigelb, Ztschr. f. physiol. Chem. **242**:43, 1936.

the mouth, nose, paws, ears and tail. This peculiar distribution led Goldberger and Lillie [6] to state the belief that this disease, hitherto called rat pellagra, was essentially identical with human pellagra. Later, however, doubt was expressed [16] as to the validity of this conception since (1) the disease can be cured by a diet of food products and concentrates that have no therapeutic value in human pellagra, (2) the lesions are not connected with gastrointestinal disturbance, as is human pellagra, and (3) photosensitivity does not play a part in the production of the cutaneous lesions. This circumstantial evidence has been confirmed by the fact that nicotinic acid, the specific antidote for both human pellagra and canine black tongue,[17] is inactive in rat pellagra.[18] The latter, accordingly, has been renamed rat acrodynia,[16] on account of its most conspicuous features. This term has been chosen without prejudice as to whether or not the underlying disease is identical with acrodynia in human beings.

Rat acrodynia is usually produced by keeping rats on a diet devoid of the vitamin B complex and supplemented with thiamine (vitamin B_1) and riboflavin. The symmetric peripheral dermatitis becomes manifest in from six to fifteen weeks in the form of red, inflamed lips and nose, hyperemic ears and red, often swollen paws. In later stages desquamation of the skin of the paws and, rather irregularly, thickening of the skin of the ears become apparent. Some brown crusting over the back is often noticeable but is generally not so prominent as the "cradle cap" appearance in egg white injury. Alopecia usually does not occur in the disease due to deficiency of pyridoxine; if it is present, at most it is slight. There is no pruritus. Abscesses form particularly around the mouth and cheeks and are localized in the follicles of the whisker hairs, which, as a rule, are retained. The abscesses are covered by scabs of varying thickness, under which ulceration may develop with

16. Birch, T. W.; György, P., and Harris, L. J.: The Vitamin B_2 Complex: Differentiation of the Antiblacktongue and the "P.-P." Factors from Lactoflavin and Vitamin B_6 (So-Called "Rat Pellagra" Factor), Biochem. J. **29**:2830, 1935.

17. Elvehjem, C. A.; Madden, R. J.; Strong, F. M., and Woolley, D. M.: Relation of Nicotinic Acid and Nicotinic Acid Amide to Canine Black Tongue, J. Am. Chem. Soc. **59**:1767 (Sept.) 1937. Fouts, P. J.; Helmer, O. M.; Lepkovsky, S., and Jukes, T. H.: Treatment of Human Pellagra with Nicotinic Acid, Proc. Soc. Exper. Biol. & Med. **37**:405 (Nov.) 1937. Smith, D. T.; Ruffin, J. M., and Smith, J. G.: Pellagra Successfully Treated with Nicotinic Acid: A Case Report, J. A. M. A. **109**:2054 (Dec. 18) 1937. Spies, T. D.; Cooper, C., and Blankenhorn, M. A.: The Use of Nicotinic Acid in the Treatment of Pellagra, ibid. **110**: 622 (Feb. 26) 1938.

18. Dann, W. J.: Nicotinic Acid and Vitamin B_2, Science **86**:616 (Dec. 31) 1937. Macrae, T. F., and Edgar, C. E.: The Water-Soluble B-Vitamins: X. Nicotinamide and Other Pyridine Derivatives in the Nutrition of the Rat, Biochem. J. **31**:2225, 1937. György, P.: Nicotinic Acid and Prevention of Nutritional Panmyelophthisis in Rats, Proc. Soc. Exper. Biol. & Med. **37**:732 (Jan.) 1938.

serpiginous defects in the skin. Blepharitis and sublingual necrotic ulcers also are not uncommon. In the advanced stages scaliness over the whole body is seen. Again, only slight or no loss of hair accompanies the formation of scales. The scales often have the appearance of an inspissated exudation which has followed hyperemia and inflammation of the skin. This exudate later takes the form of crusts or scabs, which often crack. The denuded skin then becomes visible as narrow, band-like areas which separate the remaining scales and the fur. In some animals the desquamation may take place in the form of small, dandruff-like scales which are scattered over the trunk and extremities and are pierced by the remaining hair shafts.

When suboptimal doses (5 to 10 micrograms) of pure pyridoxine are administered to rats fed the basal diet previously mentioned, improvement in the manifestations of the deficiency disease either does not occur at all or is only transitory. Furthermore, even after the administration of higher doses growth is not restored or is restored for only a short time, after which, as a rule, symptoms of relapse of the cutaneous disturbance again become noticeable.

During these stages of relapse peripheral dermatitis is in some rats overshadowed by generalized desquamation, which involves not only the trunk but frequently the whole body as well. In other rats the formation of crusts is limited to the head, especially around the eyes and cheeks. Other manifestations, such as red, inflamed lips, sticky fur over the abdomen, fine scales over the back, "spectacle eyes" and panophthalmitis, in combination or alone, complete the picture of this apparently specific entity.

When the administration of pyridoxine alone does not bring about complete cure of the cutaneous symptoms in the rats, cure can be assured [19] by the additional administration of a special separate component (or components) of the vitamin G (B_2) complex, called the filtrate factor [20] or filtrate fraction.[21] When effective treatment is interrupted,

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19. György, P.: Crystalline Vitamin B_6, J. Am. Chem. Soc. **60**:983 (April) 1938.

20. Lepkovsky, S.; Jukes, T. H., and Krause, M. E.: The Multiple Nature of the Third Factor of the Vitamin B Complex, J. Biol. Chem. **115**:557 (Sept.) 1936. Lepkovsky, S., and Jukes, T. H.: The Effect of Some Reagents on the "Filtrate Factor" (a Water-Soluble Vitamin Belonging to the Vitamin B Complex and Preventing a Dietary Dermatitis in Chicks), ibid. **114**:109 (May) 1936. Edgar, C. E., and Macrae, T. F.: The Water-Soluble B-Vitamins: VIII. Essential Dietary Factors for the Rat Present in Autoclaved Yeast Extracts in Addition to Lactoflavin, Biochem. J. **31**:886, 1937.

21. György, P.; Poling, C. E., and Subbarow, Y.: Experiments on the Anti-dermatitis Component of the Filtrate Factor in Rats, Proc. Soc. Exper. Biol. & Med. **42**:738 (Dec.) 1939.

relapse follows on an average in from two to six weeks. The relapse often has an acute, fulminant course, in which the generalized dermatitis of the type described is exhibited in a prominent form. Recent experiments [22] have shown that the cutaneous lesions which reappear after the treatment of rat acrodynia with pyridoxine or are refractory to this treatment can be cured by the administration of a crude concentrate of pantothenic acid [21] and by pure synthetic pantothenic acid.[23] Thus pantothenic acid must also be regarded as one of the vitamin factors effective in the treatment of dermatologic conditions.

These phenomena may be explained by the assumption that the experimental diet used in the production of acrodynia in rats is deficient in more than one factor, and not only in pyridoxine. Under the special nutritional conditions chosen, rat acrodynia is the predominant disease produced, but in order that it be completely cured, another missing component of the vitamin G (B_2) complex besides pyridoxine must, as a rule, be supplied.

One is reminded of the similar results encountered in the treatment of human pellagra with nicotinic acid. In most patients with pellagra nicotinic acid promptly relieves the specific symptoms. It has been stated [24] that "In a rather high percentage of the pellagrins, however, it is necessary to increase the dosage from time to time in order to keep them free from recurrences." In other patients with pellagra the additional administration of riboflavin has been found to produce complete recovery, in the same way that administration of pantothenic acid is beneficial for rats ill with the disease due to deficiency of pyridoxine.

Among the pathologic conditions in rats caused by lack of the different components of the filtrate fraction should be mentioned panmyelophthisis and hemorrhage in the adrenal glands,[25] hepatic injury [26] and

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22. György, P., and Eckardt, R. E.: (*a*) Vitamin B_6 and Skin Lesions in Rats, Nature, London **144**:512 (Sept. 16) 1939; (*b*) Further Investigations on Vitamin B_6 and Related Factors of the Vitamin B_2 Complex in Rats, Biochem. J. **34**:1143, 1940.

23. György, P., and Poling, C. E.: Pantothenic Acid and Nutritional Achromotrichia in Rats, Science **92**:203 (Aug. 20) 1940; Further Experiments on Nutritional Achromotrichia in Rats and Mice, Proc. Soc. Exper. Biol. & Med. **45**:773 (Dec.) 1940.

24. Vilter, R. W.; Vilter, S. P., and Spies, T. D.: Relationship Between Nicotinic Acid and a Codehydrogenase (Cozymase) in Blood of Pellagrins and Normal Persons, J. A. M. A. **112**:420 (Feb. 4) 1939.

25. György, P.; Goldblatt, H.; Miller, F. R., and Fulton, R. P.: Panmyelophthisis with Hemorrhagic Manifestations in Rats on a Nutritional Basis, J. Exper. Med. **66**:579 (Nov.) 1937.

26. György, P., and Goldblatt, H.: Hepatic Injury on a Nutritional Basis in Rats, J. Exper. Med. **70**:185 (Aug.) 1939.

depigmentation of the fur.[27] The last condition manifests itself in black rats as gray discoloration of the fur. This disturbance in the pigment metabolism of the fur seen in rats is independent, as a rule, of the seborrheic scaly lesions of the skin. Administration of crude concentrates of pantothenic acid [28] and even of pure synthetic pantothenic acid [23] exerts a beneficial effect on this nutritional achromotrichia in rats. The first sign of blackening of the fur is bluish discoloration of the skin, due probably to the first growth of normally pigmented hair shafts in the epidermis; then the depigmented brown, gray or white hair falls out as the new black fur appears.

Pantothenic acid, however, appears to be only one of the factors concerned in the cure of graying of the fur in rats.[28] Recently Nielsen, Oleson and Elvehjem [29] reported the isolation of a second factor belonging to this group.

There exists a definite relation between pyridoxine and dietary fat. The higher the intake of unsaturated fatty acids, or, in other words, the higher the iodine number of dietary fat, the more difficult it is to produce acrodynia in rats, with all its specific manifestations, even in spite of the complete withdrawal of pyridoxine from the diet. Unsaturated fatty acids also have a distinctly curative effect on the disease caused by deficiency of pyridoxine in the diet.[30] A satisfactory explanation of the prophylactic and therapeutic action of unsaturated fatty acids has not yet been offered, and this puzzling question is still under discussion. It appears certain, however, that there is no direct chemical relation

27. Bakke, A.; Aschehoug, V., and Zbinden, C.: A New Factor in Nutrition, Compt. rend. Acad. d. sc. **191**:1157, 1930; abstracted, Chem. Abstr. **25**:989, 1931. Morgan, A. F.; Cook, B. B., and Davison, H. G.: Vitamin B_2 Deficiencies as Affected by Dietary Carbohydrate, J. Nutrition **15**:27 (Jan.) 1938. Lunde, G., and Kringstad, H.: Ueber Veränderungen des Pelzes von Ratten durch Mangel an gewissen Faktoren des Vitamin B-Komplexes: II, Ztschr. f. physiol. Chem. **257**: 201, 1931.

28. György, P.; Poling, C. E., and Subbarow, Y.: Observations on the Factor Curative of Nutritional Achromotrichia, J. Biol. Chem. **132**:789 (Feb.) 1940.

29. Nielsen, E.; Oleson, J. J., and Elvehjem, C. A.: Fractionation of the Factor Preventing Nutritional Achromotrichia, J. Biol. Chem. **133**:637 (April) 1940.

30. (*a*) Birch, T. W., and György, P.: A Study of the Chemical Nature of Vitamin B_6 and Methods for Its Preparation in a Concentrated State, Biochem. J. **30**:304, 1936. (*b*) Richardson, L. R., and Hogan, A. G.: Skin Lesions of the Rat Associated with the Vitamin B Complex, Research Bulletin 241, University of Missouri, College of Agriculture, Agricultural Experiment Station, 1936. Birch, T. W.: The Relation Between Vitamin B_6 and the Unsaturated Fatty Acid Factor, J. Biol. Chem. **124**:775 (Aug.) 1938. Quackenbush, F. W.; Platz, B. R., and Steenbock, H.: Rat Acrodynia and the Essential Fatty Acids, J. Nutrition **17**: 115 (Feb.) 1939. Salmon, W. D.: The Effect of Certain Oils in Alleviating Localized Erythematous Dermatitis (Acrodynia or Vitamin B_6 Deficiency) in Rats, J. Biol. Chem. **123**:civ (May) 1938.

between pyridoxine, which is a water-soluble base, and unsaturated fatty acids. The mutual interdependence must be of a more indirect nature. It is significant that animal fat, especially milk fat (butter), is a rather poor source of unsaturated fatty acids and therefore does not interfere, to a great extent, with the experimental production of rat acrodynia.

In this connection it is noteworthy that symptoms suggestive of pyridoxine deficiency [31] are seen in the disease caused in rats by complete lack of fat in an otherwise well balanced diet which includes the whole vitamin G (B_2) complex. Administration of unsaturated fatty acids, sometimes termed also vitamin F, completely cures this disease.

Despite several outstanding differences in the manifestations of egg white injury and of the diseases due to deficiency of pyridoxine and pantothenic acid in rats, the common bond of the seborrheic character of some of the cutaneous lesions, at least in the gross specimen, cannot be denied. One is particularly impressed by the scaly desquamative nature of the lesions in all three of these dermatoses.

The microscopic picture of the diseases in rats due to deficiency of pyridoxine [32] and to a high proportion of egg white [33] in the diet reveals, as might be expected, the presence of acanthosis, hyperkeratosis and parakeratosis. In addition, in egg white injury there is intracellular and intercellular edema without appreciable cellular infiltration, while in the disease due to deficiency of pyridoxine the reverse is the case. The cutaneous alterations caused by lack of pantothenic acid have not yet been distinguished by histologic examination from those due to deficiency of pyridoxine.

ANALOGY OF SEBORRHEIC CUTANEOUS LESIONS IN MAN TO DISEASE CAUSED BY DEFICIENCY OF RIBOFLAVIN IN RATS

Scaly dermatoses in rats are not confined to the foregoing two, or possibly three, etiologically different diseases of nutritional origin. They may be observed [34] also in rats given a diet deficient in riboflavin, the

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31. Burr, G. O., and Burr, M. M.: A New Deficiency Disease Produced by the Rigid Exclusion of Fat from the Diet, J. Biol. Chem. **82**:345 (May) 1929; On the Nature and Rôle of the Fatty Acids Essential in Nutrition, ibid. **86**:587 (April) 1930.

32. (*a*) György, P.; Sullivan, M., and Karsner, H. T.: Nutritional Dermatoses in Rats, Proc. Soc. Exper. Biol. & Med. **37**:313 (Nov.) 1937. (*b*) Antopol, W., and Unna, K.: Pathology of B_6 Deficiency in the Rat and Response to Treatment with 2-Methyl-3-Hydroxy 4,5-Dihydroxymethyl-Pyridine (Vitamin B_6), ibid. **42**: 126 (Oct.) 1939.

33. Milbradt, W.: Experimentelle Untersuchungen zur Frage der Bedeutung des H-Vitamins für die menschliche Pathologie, Dermat. Wchnschr. **103**:1376 (Oct. 10); 1402 (Oct. 17) 1936. György, Sullivan and Karsner.[32a]

34. György, P.: Vitamin B_2 and the Pellagra-Like Dermatitis in Rats, Nature, London **133**:498 (March 31) 1934; Investigations on the Vitamin B_2 Complex: I. The Differentiation of Lactoflavin and the "Rat Antipellagra" Factor, Biochem. J. **29**:741, 1935.

first member of the vitamin G (B_2) complex that was chemically isolated and identified.[35] In this disease the symptoms are generally rather mild and consist of the appearance of small, whitish yellow, dandruff-like flakes or scales, with or without more or less symmetric loss of hair. The formation of crusts or larger scales and exfoliation are conspicuously absent. One of the most regular criteria of deficiency of riboflavin is vascularization of the cornea.[36] The condition is frequently accompanied by the formation of ulcers and resembles in all its details the clinical picture of rosacea keratitis.[37] In this connection due emphasis should be placed on the fact that rosacea is a typically seborrheic condition.

Microscopic examination [22b] of the skin of rats fed a diet deficient in riboflavin reveals the presence of hyperkeratosis of a mild degree and a slight increase in the activity of the sebaceous glands.

COMMENT

The fact that the cutaneous alterations observed in rats both with egg white injury and with the deficiency diseases caused by lack of pyridoxine, pantothenic acid or riboflavin have the common bond of the scaly desquamative type of lesions and unmistakably resemble in the gross specimen the manifestations of seborrheic diathesis in man does not provide a sufficient basis for the assumption that the relation is real and causal. On the other hand, that the respective diseases are essentially different is by no means proved by the results of histologic examinations, which show that these experimental diseases of nutritional origin in rats do not coincide in all details with the microscopic picture observed in seborrheic conditions in man.[33] The dissimilarity may be due to differences in the reactions of man and rat.

Some minor points should be mentioned here. Climatic conditions may influence both egg white injury and the disease caused by deficiency of pyridoxine. General aggravation of the egg white injury as well as of the acrodynia was often noticed on certain days in the sick rats, mainly in the spring and fall months, when there was a sudden drop in

35. György, P.; Kuhn, R., and Wagner-Jauregg, T.: Ueber das Vitamin B_2, Naturwissenschaften **21**:560, 1933; Klin. Wchnschr. **12**:1241 (Aug. 12) 1933.

36. (*a*) Bessey, O. A., and Wolbach, S. B.: Vascularization of the Cornea of the Rat in Riboflavin Deficiency, with a Note on Corneal Vascularization in Vitamin A Deficiency, J. Exper. Med. **69**:1 (Jan.) 1939. (*b*) Eckardt, R. E., and Johnson, L. V.: Nutritional Cataract and Relation of Galactose to Appearance of Senile Suture Line in Rats, Arch. Ophth. **21**:315 (Feb.) 1939.

37. Johnson, L. V., and Eckardt, R. E.: Is the Onset of Interstitial Keratitis Related to Riboflavin Deficiency? Arch. Ophth. **23**:631 (March) 1940; Rosacea Keratitis and Conditions with Vascularization of Cornea Treated with Riboflavin, ibid. **23**:899 (May) 1940. Sydenstricker, V. P.; Sebrell, W. H.; Cleckley, H. M., and Kruse, H. D.: The Ocular Manifestations of Ariboflavinosis: A Progress Note, J. A. M. A. **114**:2437 (June 22) 1940.

atmospheric pressure and in temperature.[9b] The production of acrodynia in rats is accelerated by a cold environment and is delayed by heat.[38] Albino rats proved more susceptible than black and piebald rats [39] to egg white injury. Furthermore, male rats exhibited greater sensitivity to the effect of a diet rich in egg white than did female rats.[40] The possible analogies between these reactions in rats and clinical observations in comparable conditions of the skin in man need no further comment.

In order to apply to pathologic conditions in man the experimental observations made on egg white injury and the deficiency diseases due to lack of riboflavin, pyridoxine and pantothenic acid in rats, etiologic and pathogenetic relations have to be established.

The occurrence of egg white injury is based on two conditions: (1) the toxic effect of egg white in the diet and (2) the lack of a protective or curative factor (biotin) in the diet. For the production of this disease in rats, large amounts of raw or commercial egg white are needed in the diet, while in chicks [41] a few cubic centimeters of fresh egg white suffices, provided the diet is free from biotin. Denaturalization of egg white by prolonged heating, by proteolytic digestion [42] or by intensive chemical treatment [43] deprives it of its disease-producing capacity, even when no other change in the experimental conditions is made. The conclusion seems to be warranted, therefore, and is generally accepted that the injury caused by egg white is due to a toxic effect and not to a simple deficiency. No specific toxic factor has yet been isolated from egg white. In view of this negative result and of the well known facts that raw egg white is difficult to digest and that heating and proteolytic fermentation enhance its digestibility, one is almost forced to correlate the injurious effect of egg white and its behavior in the digestive tract.[5] Thus it appears probable that the toxicity of egg white is due to undigested or—and this is more likely—to incompletely digested protein molecules which are absorbed by the intestinal wall and which then invade the blood stream to act as a more or less specific poison.

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38. György, P.: Environmental Temperature and "Rat Acrodynia," J. Nutrition **16**:69 (July) 1938.

39. Stenqvist, F.: Rohe und gekochte Hühnereier als einziges Nahrungsmittel für wachsende Ratten, Deutsche med. Wchnschr. **54**:1920 (Nov. 16) 1928. Parsons and Kelly.[6c] György.[9b]

40. Boas.[6b] Parsons and Kelly.[6c] György.[9b]

41. Ringrose, A. F.; Norris, L. C., and Heuser, G. F.: The Occurrence of a Pellagra-Like Syndrome in Chicks, Poultry Sc. **10**:166, 1931.

42. (*a*) Parsons, H. T., and Kelly, E.: The Character of the Dermatitis-Producing Factor in Dietary Egg White as Shown by Certain Chemical Treatments, J. Biol. Chem. **100**:645 (May) 1933. (*b*) György, P., and Rose, C. S.: Unpublished data.

43. Fixsen, M. A. B.: The Effect of Desiccation upon the Nutritive Properties of Egg-White, Biochem. J. **25**:596, 1931.

Distinction should be made between the primary toxic reaction and the secondary allergic reaction caused by egg white in the diet. It has been conclusively shown [44] that allergic sensitivity cannot be the underlying factor in egg white injury in rats. Here the analogy to infantile eczema and seborrheic dermatitis becomes particularly interesting. As Moro [8] has pointed out, the seborrheic manifestations in infancy are not allergic in nature but occur frequently in combination with eczema as a secondary process. In this respect the secondary eczematization of the so-called milk crust in infancy is especially significant. Furthermore, Moro [8] has emphasized the toxic character of Leiner's disease, which, with its generalized exfoliation, represents the most severe form of seborrheic dermatitis in infants.

The most common allergen in infantile eczema of the first year of life is egg white. One is tempted to relate this fact to the causation of seborrheic dermatitis, as the latter is often present simultaneously with eczema or precedes it. To attach much importance to such a coincidence would, however, be ill conceived, because the role of other allergens than egg white cannot be disregarded in infantile eczema. It is by no means rare to observe seborrheic dermatitis and eczema in an infant without hypersensitiveness to egg white and without any intake of egg white. Of course, the egg white injury could be considered [5] a nonspecific reaction due to the appearance in the blood stream of unchanged or only partially denaturalized protein molecules. The possibility then arises that other proteins, in addition to egg white, may exert the same effect, provided they also are not easily digestible, and may pass through the intestinal wall in a form that would entail the same reaction as egg white. From this point of view it should be borne in mind that seborrheic dermatitis and Leiner's disease are encountered almost exclusively in very young infants. Erythroderma desquamativum may be regarded practically as a disease of the first three months of life, with an overwhelming incidence in breast-fed infants. One is tempted to try to relate these facts to each other in the same way that the predominance of allergic conditions of nutritional origin in infancy is connected with the high permeability of the intestinal wall and immature digestive power at this age.[45] Such a conception would also explain the fact that seborrheic dermatitis as it is seen in infancy becomes more infrequent with progressing age. Furthermore, the high content of lactalbumin in breast milk makes more understandable the high incidence

44. Almon, L., and Parsons, H. T.: The Lack of Correlation Between Hypersensitivity to Egg White and Symptoms of Injury, J. Allergy **8**:547 (Sept.) 1937. György and Rose.[42b]

45. Freudenberg, E.: Physiologie und Pathologie der Verdauung im Säuglingsalter, Berlin, Julius Springer, 1929, p. 11.

of Leiner's disease in breast-fed infants, as lactalbumin,[46] next to egg white, is the most indigestible protein common in food.[46a]

Gastrointestinal disturbances and, in particular, achlorhydria, according to Schoch,[47] are not rare occurrences in adults with seborrheic conditions. In view of the presence of achlorhydria, medication with pepsin and dilute hydrochloric acid has been advocated.

For the production of egg white injury in animals, a "toxic" factor must be present and a protective or curative factor (biotin) must be lacking or present only in an insufficient amount. In man the presence of a "toxic" component is rather hypothetic, and assumption of its presence implies a generalization involving all proteins, according to their digestibility. With regard to the protective factor, the analogy between animal experiments and clinical observations seems to be closer, since it can be safely stated that the normal diet is poor in biotin content. The best and, from a practical point of view, almost the only sources of biotin in food are liver, kidney and yeast, all of which, on the whole, are not part of the usual diet. Clinical experience with the therapeutic use of different vitamins, in particular with thiamine hydrochloride, has taught that the doses of vitamins for children and adults should reach or even exceed about 1,000 rat day doses; the dose for infants should be equivalent to 400 rat day doses. A rat day dose is a biologically tested unit. One rat day dose of riboflavin, pyridoxine and biotin is contained [48] in the following amounts of yeast or liver:

	Dry Yeast, Gm.	Fresh Beef Liver, Gm.
Riboflavin	0.1 to 0.2	0.2
Pyridoxine	0.1 to 0.2	0.3
Biotin	0.3 to 0.6	0.5

Values for pantothenic acid are not yet available.

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46. Freudenberg,[45] p. 96.

46a. The views presented in the three preceding paragraphs concerning the mechanism of egg white injury may undergo changes in view of more recent developments. Since this paper was prepared it has been shown (Eakin, R. E.; Snell, E. E., and Williams, R. J.: A Constituent of Raw Egg White Capable of Inactivating Biotin in Vitro, J. Biol. Chem. **136**:801 [Dec.] 1940) that egg white contains an albumin-like protein fraction which is capable of forming with biotin a stable and apparently practically indigestible compound. Unpublished experiments carried out by the author in collaboration with R. J. Williams and R. E. Eakin were in agreement with this new assumption. Addition of the "toxic" albumin fraction of egg white to a basal diet containing "detoxified" cooked egg white restored the toxic quality of the diet.

47. Schoch, M. A.: Die Behandlung des Status seborrhoicus mit Säure-Pepsinpräparaten, Schweiz. med. Wchnschr. **65**:656 (July 20) 1935.

48. Birch, György and Harris.[16] György.[9b]

It is interesting that liver and yeast are the best sources of riboflavin and pyridoxine, as well as of biotin. Riboflavin and pyridoxine, however, are more widely distributed in common foodstuffs than is biotin. Nevertheless, the usual diet probably has a low content of riboflavin and is not rich in pyridoxine. Liver, kidney, yeast and cow's milk are the only food products that are rich in riboflavin. Meat, vegetables, cereals and even wheat germ, bran and rice polishings contain small, almost negligible amounts. One curative rat day dose of riboflavin requires the supply of from 1 to 5 Gm. of these foodstuffs. The content of pyridoxine in foodstuffs in general is higher than the content of riboflavin in the same foodstuffs, with the noteworthy exception of egg white, which is rich in riboflavin but devoid of pyridoxine. The predominance of pyridoxine over riboflavin is most pronounced in wheat germ, rice polishings, cane molasses, bran and fish, whereas in meat, vegetables, the endosperm of cereals and even liver, kidney and yeast the difference is not pronounced.

Pyridoxine can be to a large extent, but not completely, extracted [49] from foodstuffs that contain it, whereas biotin in its natural state in liver, kidney and yeast is almost completely insoluble in water and can be obtained in water-soluble form only by proteolytic digestion or by hydrolysis at high pressure.[50] Commercial preparations of vitamin factors are aqueous extracts or pressed juice from liver or yeast. They are thus devoid of biotin and exhibit only part of the pyridoxine potency originally present in liver and yeast. Furthermore, it is conceivable that gastrointestinal disorders may interfere with the liberation and subsequent absorption of biotin and pyridoxine from the food products that contain them.

Only one really common foodstuff, cow's milk, is rich in both pyridoxine and riboflavin [51] and also contains appreciable amounts [9b] of biotin. One rat day dose is represented by the following average amounts of cow's milk and of human milk:

	Cow's Milk, cc.	Human Milk, cc.
Riboflavin	5 to 10	15 or more
Pyridoxine	5 to 10	5 to 10
Biotin	10 to 20	more than 25

49. Kuhn, R., and Wendt, G.: Ueber das antidermatitische Vitamin der Hefe, Ber. d. deutsch. chem. Gesellsch. **71**:780, 1938. Birch and György.[30a]

50. Lease, J. G., and Parsons, H. T.: The Extraction of the Factor Curative of Dermatitis in Rats Due to Egg White; abstracted, J. Biol. Chem. **105**:1, 1934. György (footnote 9 *a*, and *b*).

51. György, P.: Quantitative Estimation of Lactoflavin and of Vitamin B_6 in Cow's Milk and in Human Milk, Proc. Soc. Exper. Biol. & Med. **35**:204 (Oct.) 1936.

The fact that the content of biotin in human milk is low could serve to corroborate the views presented earlier in this paper concerning the high incidence of Leiner's disease in breast-fed infants.

The milk intake of children, and especially of adults, is lower than that of infants, absolutely or at least relatively in proportion to body weight. It can therefore be disregarded as a potent source of the vitamins in question.

From the foregoing comments it may be assumed that in infancy the nutritional conditions and the state of the digestive tract would rather favor the mechanism of deficiency of biotin, whereas in later age periods chronic hypovitaminosis with respect to all four vitamins discussed may be considered a possible cause.

Experiments on rats have demonstrated that there is a preparatory period lasting as long as from six to fifteen weeks before the first manifestation of egg white injury or of total deficiency of pyridoxine and riboflavin becomes apparent, under the most severe conditions of total withdrawal of the vitamins concerned from the diet. The preparatory period for hypovitaminosis in rats may last from twenty to thirty weeks or more. Moreover, the manifestation of deficiency diseases in general, and in particular those due to lack of biotin, pyridoxine, pantothenic acid and riboflavin, is considerably delayed in adult animals as compared with animals that are still growing. In the light of these experimental results and of the fact that the life cycle of man is from twenty to twenty-five times longer than that of the rat, it is certainly conceivable that the preparatory period for seborrheic manifestations in man on the basis of a partial nutritional deficiency may involve several years, and even decades.

Barber [52] has stated that in man "Of all diatheses the seborrheic one is probably the commonest." The incidence is estimated to be as high as 30 to 50 per cent of the population of the civilized countries in the temperate climate.

The common occurrence of rosacea in alcohol addicts may raise the question whether rosacea should be considered a deficiency disease rather than a toxic manifestation, in analogy with polyneuritis, pellagra and cirrhosis of the liver associated with alcoholism. In this connection one is reminded of experimental rosacea keratitis observed [36b] in rats fed a diet deficient in riboflavin and of the successful clinical treatment of rosacea keratitis [37] in man by the administration of riboflavin.

Excess of starchy food, overfeeding in general and, less frequently, excess of fat and protein have been suspected in the past by various der-

52. Barber, H. W.: Lettsomian Lecture on the Relationship of Dermatology to Other Branches of Medicine, Lancet **2**:363 (Aug. 24) 1929.

matologists of being responsible for seborrheic diathesis. In the assumption of causes such as these, however, the common bond of hypovitaminotic conditions is ignored, and there is no general agreement with clearcut therapeutic results. The interrelation between proteins and biotin, on the one hand, and between fats and pyridoxine, on the other, is well established from animal experiments and has already been discussed. Carbohydrates [53] of varying origin also have distinctly different effects on the production of the disease due to deficiency of pyridoxine in rats. The reputed influence of unilateral excess of protein, fat or carbohydrate on seborrheic conditions in man would seem to be in agreement with these animal experiments.

Administration of yeast and liver has long been advocated in the clinical treatment of seborrheic and similar conditions of the skin. The use of yeast in dermatologic diseases can be traced to ancient times and is still mentioned in textbooks in connection with the therapy of furunculosis, acne vulgaris, alopecia, rosacea or psoriasis. On the whole the results reported are far from satisfactory, and yeast, consequently, is not regarded as a reliable medication. The explanations given for its supposedly beneficial effect are rather vague, and the possible relation of its efficacy to its vitamin content is scarcely mentioned. Such an omission is understandable, of course, when it is realized that what is known of the vitamin B complex, one of the best sources of which is yeast, is of recent date.

Liver was mentioned by Czerny and Keller [54] in 1913 for the prophylactic and therapeutic treatment of exudative diathesis in infants; since that time it has been considered a valuable dietetic measure.[55] Czerny emphasized the value of the high content of purine substances in liver, in contrast to the low content of purine substances in the milk diet generally used for infants, and he was inclined to conclude that this fact provided the pharmacologic basis of liver therapy in exudative diathesis. In pediatric practice liver is given mainly in the form of liver purée.

53. Chick, H.; Copping, A. M., and Edgar, C. E.: The Water-Soluble B-Vitamins: IV. The Components of Vitamin B_3, Biochem. J. **29**:722, 1935. Bender, R. C.; Ansbacher, S.; Flanigan, G. E., and Supplee, G. C.: The Influence of Dextrin and Sucrose on Growth and Dermatitis, J. Nutrition **11**:391 (May) 1936.

54. Czerny, A., and Keller, A.: Des Kindes Ernährung, Ernährungsstörungen und Ernährungstherapie, ed. 1, Leipzig, Franz Deuticke, 1913, vol. 2, p. 372; ed. 2, 1923, vol. 1, p. 435; 1928, vol. 2, p. 372.

55. Stolte, K.: Die exsudative Diathese, in Klemperer, G., and Klemperer, F.: Neue deutsche Klinik, Berlin, Urban & Schwarzenberg, 1929, vol. 3, p. 289.

That administration of liver extract is beneficial in acne vulgaris and furunculosis [56] and in psoriasis [57] has also been claimed.

The fact that the use of neither yeast nor, apparently, liver has been given unanimous support as a therapeutic-dietetic agent in medical practice will appear in a new light when the question of dosage is considered. According to the values given previously in this paper, the minimum daily therapeutic dose of the vitamins in question, computed on the basis of the rat day dose, will be found in ½ to 1 pound (225 to 450 Gm.) of dry yeast and of fresh liver. It is evident that the regular intake of the dose required cannot be forced in practice. Administration of such a large dose of liver has never been attempted; adults would not find even the minimum daily dose easy to take. Consequently it is not surprising that insufficient doses have proved of inconstant value in clinical trials; nor does this observation nullify the attempt to draw an analogy between seborrheic conditions in man and in rats.

As further indirect proof in favor of such a conception, attention may be called to the beneficial effect derived from administration of a liver preparation rich in biotin. It is used in Germany under the name of murnil in the treatment of seborrheic eczematous manifestations and of various pathologic conditions of the fur in dogs.[58] The widespread use of liver in different brands of dog food should also be mentioned.

It would seem justifiable to attempt direct clinical therapeutic trials in order to prove the practical value of the impressions gained from the animal experiments.

SUMMARY

Pellagra is only one of the conditions involving the skin and connected with the members of the vitamin G (B_2) complex and is due to a deficiency of nicotinic acid in the diet.

Attention is called to the seborrheic character of various cutaneous manifestations in rats caused by the lack of other members of the vitamin G (B_2) complex in the diet. These experimentally produced lesions characteristic of lack of biotin (vitamin H), pyridoxine (vitamin B_6), pantothenic acid or riboflavin are described in detail.

The question of the etiologic and pathogenetic relation of these deficiencies in the diet of the rat is discussed, with particular reference

56. Sutton, R. L.: Liver and Diet in Acne Vulgaris and in Furunculosis, Arch. Dermat. & Syph. **18**:887 (Dec.) 1928.

57. Spiethoff, B.: Erfahrungen mit der Lebertherapie bei Intoxikationszuständen nach Salvarsan, Wismut, bei Infektionen und Psoriasis, München. med. Wchnschr. **76**:577 (April 5) 1929. Grüneberg, T.: Die Lebertherapie der Psoriasis, Dermat. Wchnschr. **97**:1793 (Dec. 23) 1933.

58. Berndt: München. tierärztl. Wchnschr., 1935, vol. 86, no. 2. Wand: Berl. tierärztl. Wchnschr., 1935, vol. 24, no. 369.

to the occurrence of "seborrheic diathesis" in man and the possibility that the latter has a nutritional foundation.

Liver and yeast, which have been and still are used in the treatment of various pathologic conditions of the skin, are considered to be mainly sources of members of the vitamin G (B_2) complex. The quantitative point of view is particularly stressed, and emphasis is placed on the fact that the doses of yeast and liver commonly advocated in clinical treatment appear to be far below the minimum requirement computed from animal experiments. The clinical implications of the experimental results for the "seborrheic state" in man are also discussed, with particular reference to therapeutic possibilities.

DERMATITIS HERPETIFORMIS

INFLUENCE OF AGE ON INCIDENCE AND TYPE OF LESIONS

M. H. GOODMAN, M.D.
BALTIMORE

Observations have been made with respect to the types of cutaneous lesions which are apt to predominate in patients with dermatitis herpetiformis at certain age levels.

It has been brought out by Brocq [1] that the peaks of incidence in dermatitis herpetiformis apparently fall at about the age of 20 and at about the age of 60. On the other hand, Zieler [2] recently noted that the greatest incidence of pemphigus is between the ages of 30 and 50 years.

Reports by several authors were studied to note the age of each patient and his or her predominant type of lesion. Reports of the disease in children were excluded from this study. In compiling the data, the patients were divided into two age groups, one ranging from 16 to 49 years and the other from 50 and over. A review of the literature shows that in patients 50 years of age or older the tendency is to manifest predominantly, although not as strikingly as in children, a vesiculobullous type of dermatitis herpetiformis with large bullae, varying from 1 to 5 cm. or more in diameter. In patients ranging in age from 16 to 49 polymorphous lesions associated with small (pinhead-sized to pea-sized) vesicles and bullae predominate.

I have encountered in the past four years 8 cases of dermatitis herpetiformis in persons well over the age of 50, all of whom exhibited essentially a pure vesiculobullous type of eruption with large bullae predominating. The records of 12 cases of dermatitis herpetiformis in adults at the Johns Hopkins Hospital showed, with a single exception, the same tendency, i. e., tiny vesicles and small bullae in the young adult group and large bullae in the old adult group. Hitherto there has been no special mention made in the literature of this apparent tendency of

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From the Department of Dermatology, Johns Hopkins University School of Medicine.

Read before the Section on Dermatology and Syphilology at the Ninety-First Annual Session of the American Medical Association, New York, June 12, 1940.

1. Brocq, L.: De la dermatite herpétiforme de Duhring, Ann. de dermat. et syph. **9**:1, 65, 133, 209, 305, 433 and 493, 1888.

2. Zieler, in discussion on Lutz, W.: Pathogenese und die Aetiologie der Pemphigusgruppe, Schweiz. med. Wchnschr. **19**:778 (July 9) 1938.

the disease to manifest itself by large bullae in elderly persons. There has evidently also been a lack of awareness of the relative frequency of its occurrence in this age group. For these reasons, together with the fact that the large bullous type of the disease offers the problem of differential diagnosis with respect to pemphigus, I deemed it appropriate to report briefly 4 of the 8 cases.

REPORT OF CASES

CASE 1.—Mrs. S. B., a Russian-born American housewife aged 60, with senile arteriosclerosis but otherwise in good health, had a pruritic bullous eruption about the genitals, which developed in early January 1937. The eruption was characterized by intolerable itching limited only to the areas of involvement, which at first were only the genitalia, the pubic area, the crural folds and the adjacent inner surfaces of the thighs. There were rapidly successive attacks of discrete, occasionally coalescent, tense-walled, deep-seated vesicles and bullae, varying in size from that of a pea to that of a cherry and of a walnut. Later in the course of the disease such isolated groups appeared spasmodically in the axillas, on the midportion of the legs and, rarely, in the mouth.

The differential blood count showed: neutrophils 48 per cent, juvenile cells 6 per cent, eosinpohils 13 per cent, lymphocytes 26 per cent and mononuclear leukocytes 7 per cent. A culture of bullous fluid was sterile, and smears showed 90 per cent eosinophils and the remainder lymphocytes.

No appreciable improvement resulted from subcutaneous injections of moccasin venom, in a dilution of 1 : 3000 (Lederle) or from sulfanilamide. On April 1, 1937, solution of potassium arsenite U. S. P. was administered, 4 minims (0.25 cc.), thrice daily, increasing 1 minim (0.06 cc.) daily. When the dose reached 7 minims (0.4 cc.) it was reduced to 4 minims thrice daily and the administration continued. Accompanying this therapy one-quarter erythema dose (75 r) of roentgen rays (unfiltered) was given to the involved regions at weekly intervals. In the third week of this regimen, the lesions began to decrease in number, and six weeks later, about June 7, the skin was free from eruption except for some pigmentation. The arsenical therapy was then discontinued, and the patient has remained free from eruption since (three and one-half years).

CASE 2.—A Russian-born Jewish woman aged 57 when first seen, in early October 1938, presented a severely itching eruption of one month's duration, composed of palm-sized groups of vesicles and bullae, located on the proximal third of each arm, the outer aspect of the midportion of each thigh, the ankles and the dorsa of the feet. During the succeeding ten weeks there were rapidly recurring attacks consisting of a central large bulla, ranging in size, in different areas, from that of a lima bean to that of a cherry or of a walnut, surrounded by a few vesicles and smaller bullae, ranging up to the size of a cherry. A differential blood count at the height of an attack showed eosinophilia (7 per cent eosinophils). This patient responded well to the administration of solution of potassium arsenite U. S. P., as in case 1.

CASE 3.—E. T., a well nourished and developed, intelligent mulatto widow 75 years of age, with a thin but well preserved skin, when first seen on July 8, 1935, had been having repeated attacks of blisters on the chest for one month. Under each breast there was a palm-sized irregular ring-shaped group of moderately thick-walled, flaccid, rather easily ruptured bullae, the average size of which was

that of a cherry. The inner margin of the ring was encircled by a narrow, faintly elevated zone of redness and the outer by a similar but broader and slightly more elevated zone. On the left breast and on the right side of the abdomen there was a similar patch. The patient did not complain of any appreciable itching, and the lesions showed a tendency to fairly rapid involution.

The blood smear showed a differential count of 61 per cent polymorphonuclear leukocytes, 32 per cent lymphocytes and 7 per cent monocytes.

The patient has continued until the time of writing (four years), with little or no remission, to have lesions develop at various sites, symmetrically and nonsymmetrically. Sulfapyridine was not tolerated. The improvement which seemed to result from solution of potassium arsenite U. S. P. was short lived. The lesions varied from groups of discrete split pea-sized to pea-sized vesicles to irregularly and circularly arranged bullae varying in size from that of a white bean to that of a cherry and slightly larger. During the most recent period of observation the bullae were superficial and thin walled, with a tendency to rapid clouding of their contents, early rupturing and rapid involution and healing.

Case 4.—L. S. H., a white widower aged 68, of Russian birth, had been in good general health until the latter part of September 1938, when intense itching of the skin developed. Examination seven weeks after the onset of his eruption revealed an extensive lichenoid and eczematoid process involving the entire back from the shoulders to the hips and also the arms, the inner aspects of the thighs and the anterior surfaces of the legs. This eruption followed intense and persistent scratching and rubbing because of universal intolerable itching. The extensor aspects of the forearms and the dorsa of the hands were covered with numerous discrete tense-walled deep-seated vesicles and multilocular bullae, most of which showed a red halo but some of which arose on normal skin. The lesions were intensely pruritic, and although many averaged in size that of a coffee bean, most of them reached the size of a cherry or of a walnut or were even larger. On the anterior aspects of the thighs a central large bulla was surrounded by clusters of smaller bullae, varying in size. The skin of the chest, abdomen and flanks was essentially normal in appearance. The blood smear showed the following differential count: neutrophils 59 per cent, eosinophils 21 per cent, basophils 1 per cent, lymphocytes 9 per cent, mononuclear leukocytes 7 per cent and juvenile cells 3 per cent.

Sulfanilamide therapy produced a hemolytic anemia; high colonic irrigations were not beneficial, and solution of potassium arsenite U. S. P. and sodium cacodylate were not tolerated. On December 12 an initial subcutaneous injection of moccasin venom (Lederle), 0.2 cc., was given, and the dose was increased daily by 0.1 cc. until December 17, when a dose of 0.8 cc. was given and on each of the three succeeding days 1 cc. At this point there was decided improvement in the eruption. The eosinophilia of the blood, which had varied on frequently repeated examination, with from 18 to 21 per cent eosinophils, was absent on December 15. On the other hand, the urea content of the blood, which originally was normal with some slight fluctuation, increased so that on December 19, when the skin was free of active lesions, it was 65.91 mg. per hundred cubic centimeters.

After two weeks there was a recurrence of bullous lesions, and thenceforth there were rapidly recurring attacks. From time to time one or more moderate-sized blebs with an accompanying red halo would appear on the eyelids or lips but never in the mouth. The itching was uncontrolled by various lotions, ointments, bran, sulfur (solution of sulfurated lime N. F.) and potassium permanganate (1:5,000) baths.

During the active phases of the disease, marked by formation of bullae, repeated differential blood counts showed the eosinophil count to range from 13 per cent to a maximum on one occasion of 63 per cent. On June 3, 1939 treatments were begun with viosterol in oil [3] and thereafter 350,000 U. S. P. units of vitamin D was given daily in divided doses. After one week of this therapy there was pronounced involution of the bullae, and the disease was well under control by July 13, 1939. Complete prevention of the formation of bullous lesions was effected from that time on by the daily administration of 150,000 U. S. P. units of vitamin D. However, there was a rather continuous increase in the urea content of the blood, which amounted to 77.9 mg. per hundred cubic centimeters on August 3. Against advice, on September 25 he was removed from the hospital to his home, where pneumonia developed and he died ten days later.

COMMENT

The cutaneous disease in case 4 had been well controlled apparently with large doses of vitamin D, but cardiovascular and renal disease with uremia led to a fatal pneumonia. The other 7 patients are still under observation at the time of writing. The ages at the time of onset of the disease of the 4 patients whose histories are not included were 59, 62, 68 and 71 years. The duration of the dermatosis before I first saw the patients varied from five months to two years. All of them maintained good general health and as a rule were active in spite of the appearance, in rapidly successive attacks, of customarily grouped, intensely pruritic lesions, composed chiefly of moderate-sized and large bullae. Aside from routine general measures, all of these patients benefited at one time or another from the administration of solution of potassium arsenite U. S. P. (as reported in case 1) and from fractional roentgen ray therapy. The administration of viosterol was tried because of its reputedly good effects in some cases of pemphigus.[4] In 2 of the 4 patients large doses of this vitamin (administered as reported in case 4) seemed to influence the disease favorably during one month of therapy.

The 8 elderly persons with dermatitis herpetiformis encountered in the past four years included 4 Jews, 1 German, 2 of English descent and 1 mulatto woman. There were 6 women and 2 men. In the same period I saw a total of only 4 patients who were young or middle-aged adults, 1 infant and a 12 year old girl. I think the disease is more common in persons around the age of 60 than is generally believed, and I am in agreement with Zieler,[2] that a peak of incidence falls at this late

3. The viosterol in oil employed was prepared by the Sperti process and supplied in capsules, each containing 50,000 U. S. P. units of vitamin D, by the William S. Merrell Company, Cincinnati.

4. (*a*) King, H., and Hamilton, C. M.: Pemphigus Controlled by Vitamin D, Arch. Dermat. & Syph. **39**:515 (March) 1939. (*b*) Tauber, E. B., and Clarke, G. E.: Treatment of Pemphigus with Concentrated Viosterol, ibid. **40**:82 (July) 1939.

age period. The diagnosis may not be made unless it is borne in mind. Stümpke [5] emphasized the fact that the diagnosis may be missed because of the occurrence of the abortive forms of the disease which simulate urticaria or eczema. Furthermore, it must be remembered that the patient may have attacks in which the lesions are localized or short lived or which are modified by secondary factors. This point is well illustrated by 1 of my patients, a 62 year old woman, whose attacks, of two years' duration, were limited most frequently to the legs. I saw her a number of times with a circinate group of large bullae at these sites, but on several occasions when I demonstrated her to colleagues there were only secondary superficial eczematoid changes, which led to a diagnosis of eczema. However, the colleagues were eventually convinced that she had dermatitis herpetiformis when she appeared with a fresh attack, which included, in addition to the groups of large bullae on the legs, symmetric groups of vesicles on the elbows and knees. The eruption occurred in rapidly successive attacks and was intensely pruritic; the bullous contents showed 95 per cent eosinophils, and the condition responded so well to treatment with solution of potassium arsenite U. S. P. that the patient asked for this medication whenever a relapse occurred. With regard to all the other 7 patients, every experienced dermatologist who saw them agreed on the basis of the clinical picture, course and thorough laboratory studies (including biopsy) that the condition was typical of dermatitis herpetiformis.

SUMMARY

Personal experience in the past four years with 8 cases of dermatitis herpetiformis in elderly persons and the data obtained from the study of a few groups of collected cases of this disease in the literature would seem to indicate that there is a greater tendency to the occurrence of mixed and small vesicular lesions in young and middle-aged adults than in elderly persons. In the latter the disease is more prone to manifest itself by large vesicles and bullae. My experience also seems to indicate that one peak of incidence of dermatitis herpetiformis falls around the age of 60 years. The conclusion is suggested that such observations may be of some import, even if slight, in the differential diagnosis with respect to pemphigus.

Since the age of the skin apparently has a bearing on the type of lesions and the size of the bullae in dermatitis herpetiformis, it is suggestive that other as yet unknown cutaneous factors may also be influential in the causation of this disease.

420 Medical Arts Building.

5. Stümpke, G.: Einige Ausführungen über Dermatitis herpetiformis Duhring, Med. Klin. **35**:1399 (Oct. 27) 1939.

ABSTRACT OF DISCUSSION

DR. ISADORE ROSEN, New York: When a classic case of dermatitis herpetiformis is presented a student can make a diagnosis from the clinical features alone. The histologic picture, too, conforms with the usual description and offers no difficulties. But, as in other cutaneous conditions, when the disease does not run true to type clinically, the microscope often fails to aid in the interpretation.

If vesicular or bullous lesions, grouping of lesions, pruritus, pigmentation, chronicity and eosinophilia are pathognomonic of dermatitis herpetiformis, then a number of other conditions should be included with this disease, even though they do not present the picture originally described by Dr. Duhring. Therefore, the classic examples must be separated from the atypical ones.

If one analyzes the cutaneous diseases seen in both the clinic and the hospital, the conclusion is reached that classic forms of dermatitis herpetiformis are rare. In 1939 at the Skin and Cancer Unit of the New York Post-Graduate Medical School and Hospital 20,000 new patients were admitted. Of this number, I found that in only 24 instances was the diagnosis of dermatitis herpetiformis considered among such conditions as bullous erythema multiforme, pemphigus, drug eruptions and various types of allergic and toxic eruptions. In 8 of these cases it was impossible to complete investigations because of only one visit. Of the remaining 16, in only 2 cases was a diagnosis of dermatitis herpetiformis made without question by expert clinicians. In 1 there were 7 per cent eosinophils and in the other 1 per cent. In the other cases there was no increase in eosinophilia. Biopsy resulted in only one pathologic diagnosis of dermatitis herpetiformis, the rest being reported as toxic eruption, contact dermatitis or chronic dermatitis.

It is only occasionally that one is called on to differentiate between dermatitis herpetiformis, pemphigus or bullous erythema multiforme. If a definite diagnosis could be established by the method suggested by Dr. Goodman, it would be of great value. One clinical feature of significance in the differential diagnosis is pigmentation. It is not often associated with pemphigus unless due to concomitant treatment, while it is practically constant in dermatitis herpetiformis. Of course, it may be a symptom of many dermatoses, especially pruriginous ones. I wonder whether Dr. Goodman extended his investigations to the pigmented areas and, if so, how his findings compared with those in the nonpigmented ones.

I have not been satisfied with the results of the administration of potassium iodide or of the iodide patch test in establishing a diagnosis of dermatitis herpetiformis. When this test was first described, my associates and I carried on a series of investigations, with only indifferent results. In 1 instance in which we applied the test to a patient with classic dermatitis herpetiformis, the lesions, instead of becoming aggravated, cleared up, and we continued administration of the drug, with marked improvement in the eruption.

I called attention to a disease which is associated with a great increase in eosinophils in the blood and frequently in the tissues in the ARCHIVES OF DERMATOLOGY AND SYPHILOLOGY (**32**:962 [Dec.] 1935); later the subject was written up by Drs. Sulzberger and Garbe (Nine Cases of Distinctive Exudative Discoid and Lichenoid Chronic Dermatosis, ARCH. DERMAT. & SYPH. **36**:247 [Aug.] 1937). The clinical features in the patients with this condition, whose ages range between 18 and 30 years, would fit in with those described by Dr. Goodman in his younger group, namely, pinhead-sized vesicles occurring in groups, often disseminated over the entire body and very pruriginous, at times giving the picture of an allergic dermatitis. It is in these patients that decided eosinophilia is found, sometimes with as high as 40 per cent eosinophils; the high value persists until there is a decided improvement in the clinical

manifestations, when it gradually reduces to a lower level, only to rise again with a recrudescence of the disease. The itching is intense; the pigmentation is pronounced, in some to an extreme degree, and the disease is resistant to all forms of therapy. It may be that the condition in these cases constitutes an atypical form of dermatitis herpetiformis, the causative factor of which may be a skin determinant, and it seems to me that it would be worth while to apply the test as described by Dr. Goodman to these patients.

In addition to the therapeutic measures mentioned by Dr. Goodman, such as arsenic, roentgen rays, vitamins, sulfanilamide and potassium permanganate baths, I have also had a certain amount of success with fever therapy and autohemotherapy in a number of cases.

Dr. Jacob H. Swartz, Boston: I want to mention a small group of patients that I have followed for the past five years with intradermal tests with Streptococcus faecalis and colon bacilli obtained from the stools of patients with dermatitis herpetiformis, and I found the following results: The test with Str. faecalis elicited no reaction whatsoever, while I was able to reproduce lesions clinically simulating dermatitis herpetiformis at the point of injection with the colon bacillus.

I gave these patients the injections in graduated doses, first intradermally and then subcutaneously, up to 1 cc., and found that coincidentally with this both subjective and objective symptoms disappeared. After an intradermal test with the colon bacillus, there was no such reproduction of the lesions. Dermatitis herpetiformis later recurred, and similar results have been found with both intradermal tests and therapy. I tried similar injections in 2 cases of pemphigus but there was no reproduction of the lesions.

I have not done sufficient study to establish any claims, but I think the method is worth considering, especially when sulfanilamide happens to be a valuable drug in dermatitis herpetiformis.

Dr. Henry D. Niles, New York: I have been especially interested in dermatitis herpetiformis for some time. I have been able to collect a series of 37 patients in the course of three or four years. Their ages range from 7 years to 63. The average age was 37 years. I think that the results of laboratory tests have been entirely too much stressed in cases of dermatitis herpetiformis. In this series, the average proportion of eosinophils in the blood was only 3.11 per cent, which is extremely low. I noticed in the third case of Dr. Goodman's that the eosinophil count of the blood ranged from 0 to 2 per cent.

I have had the same experience as Dr. Rosen with the potassium iodide patch test. In many or most of these 37 patients the condition was typical clinically and histologically, and yet the majority failed to react to a patch test with a 50 per cent solution of potassium iodide.

I also had the same experience with 1 patient as Dr. Rosen. I administered potassium iodide in order to aggravate a supposed dermatitis herpetiformis, and the eruption cleared up promptly and the patient asked for more of the drug. Later, without the potassium iodide, typical dermatitis herpetiformis developed, which was proved histologically. In view of the iodide sensitivity, I thought theoretically that there might be some thyroid disturbance in patients with dermatitis herpetiformis, and I have taken the basal metabolic rates of most of the patients. Some of them were fairly high, but not consistently so. Those whose rate was at least above + 5 per cent (some were as high as + 20 or + 25 per cent, but without hyperthyroid symptoms) I referred to the department of roentgenotherapy for treatment of the thyroid gland with filtered roentgen rays of high voltage, checking the basal metabolic rate at frequent intervals. In some of these

patients it was interesting to observe that as the basal metabolic rate went down, the symptoms of dermatitis herpetiformis improved. The improvement, however, was temporary, and after the basal rate was down to 0 or —5 or —10 per cent or even lower, roentgen therapy was stopped. Promptly the improvement ceased and the patient had a recurrence, which was the result of every other form of therapy also.

I think that there may be something wrong with the technic followed so far, but there is some hope of logical treatment in this direction. Certainly all the treatment used at present is more or less empiric and temporary. Arsenic and local roentgen therapy are potentially dangerous if persisted in too long.

Dr. Theodore Cornbleet, Chicago: In studies on dermatitis herpetiformis, I made day to day observations, among which I included the determination of capillary permeability, inorganic constituents of the blood and histamine and epinephrine flares. The main conclusion from this work was that in persons with dermatitis herpetiformis there is fluctuation and instability as compared with normal persons and those with some other disorders. This instability is also characteristic of one other disorder, namely, allergy. In the latter, too, the eosinophils are increased.

Now I do not feel that dermatitis herpetiformis is by inference a disorder related to allergy, because eosinophils may be increased in number wherever there is absorption of body fluids. Extravasated blood may increase the number of eosinophils, and they may become multiplied in trachina, probably due to injury and absorption of muscle tissue. Eosinophils are increased in number with injection of histamine; as a matter of fact, at the site of injections of histamine the eosinophils soon are increased in number. Incident to the injection of histamine itching occurs or is increased. It might be of value to examine the blisters in dermatitis herpetiformis and assay the material for its histamine content. It is very likely that this constituent would be found to be increased.

There is another point about the eosinophils which is often overlooked, and that is that spleen extract will cause a reduction in the number of them. This condition is rather temporary, and the continued administration of the spleen extract does not cause a progressive reduction in the eosinophils. The reduction of the eosinophils by the spleen extract, on the other hand, does not cause parallel clinical changes. The mere presence or absence of eosinophils or their decrease in number does not necessarily, therefore, indicate a kind or degree of clinical condition in the patient.

The entire matter of the eosinophils will remain somewhat speculative until some means can be found for separating eosinophils from the blood in sufficient numbers so that controlled experimental work can be conducted with them.

Dr. M. H. Goodman, Baltimore: No effort was made to test the response of the skin in regard to eosinophils in residual pigmented areas. It would be interesting to make such studies.

Dr. Rosen referred to the possibility that lichenoid and discoid dermatitis, described by Sulzberger and Garbe, may be a form of dermatitis herpetiformis. I cannot see a resemblance between these two diseases. It would, however, be interesting to see what artificial blisters would show with respect to eosinophils in that disease, in view of the purported high eosinophilia of the blood in some cases.

Dr. Swartz refers to the beneficial effects of autogenous colon bacillus vaccine in cases of dermatitis herpetiformis. This work calls to mind the theory of some

older authors that this disease is caused by intestinal toxemia. In my cases attention to the state of the bowel did not appreciably influence the course of the disease.

In my cases the basal metabolic rates were perfectly normal. Dr. Cornbleet refers to the allergic factor in dermatitis herpetiformis. It is my impression that allergy may be simply a nonspecific incidental or precipitating factor in dermatitis herpetiformis.

Since I first became interested in the aspects of dermatitis herpetiformis presented in my paper four years ago, when I encountered my first patient (case 1), I have observed 8 cases of this disease in elderly persons and only 4 proved cases of dermatitis herpetiformis in young adults. I should therefore like to emphasize my belief that the disease is more common in persons around the age of 60 than is customarily believed. Furthermore, my experiences would bear out the impression that a peak of incidence falls at about the age of 60. All of my patients were of a poor class but were intelligent and lived in environments productive of marked emotional strain, worry, self neglect and undue responsibility. In case 1 the advent of the eruption coincided with a recurrent episode of dementia praecox in the patient's son which required institutionalization. Such facts would lead one to postulate some neurocutaneous disturbance as basic in the etiology and pathogenesis of dermatitis herpetiformis. From a consideration of the clinical and laboratory data which I have outlined in my paper I cannot but view the disease as representing a special irritability of the skin and am inclined to place the blame for the disease on the patients' skin rather than on some as yet undiscovered invading agent or agents.

In addition to data which I have already presented bearing on the phenomenon of special irritability of the skin in dermatitis herpetiformis, other findings would seem confirmative. For example, Natase (Natase, G.: Dermatite herpétiforme Duhring-Brocq de cause iodique, *Rev. méd.-chir.* **49**:63, 1938) found in his well studied case that previously involved areas of the skin were more sensitive to iodides than uninvolved areas. I have found that cantharides-produced blisters on the sound skin of involved areas are invariably larger than those on uninvolved regions in equivalent periods of time.

I may emphasize that dermatitis herpetiformis in elderly persons is more common than is ordinarily believed and that this diagnosis should be borne in mind. Stümpke emphasized the fact that the diagnosis may be missed because of the occurrence of the abortive forms of the disease that simulate urticaria and eczema or dermatitis. Furthermore, it must be remembered that a patient may have attacks in which the lesions are too localized or too short lived or which are modified by secondary factors so that the correct diagnosis escapes one.

OCCUPATIONAL DERMATITIS IN CIGAR MAKERS DUE TO CONTACT WITH TOBACCO LEAVES

REPORT OF THREE CASES

FRANK VERO, M.D.
NEW YORK
AND
SERAFINO GENOVESE, M.D.
DANBURY, CONN.

Industrial physicians dealing with tobacco workers were acquainted with the occupational diseases of the gastrointestinal tract, organs of respiration, nervous system and mucous membranes of the eyes due to the tobacco dust and vapor. Diseases of the skin were observed but occasionally. The dermatoses most frequently described were those produced by traumatism, foreign bodies, inflammatory infections, felons, cellulitis and alteration of the nails.

Dermatitis of tobacco workers due to contact with tobacco leaves has been only infrequently observed. White,[1] Oppenheim, Rille and Ullmann [2] and Schwartz and Tulipan [3] all emphasized the scarcity of cases of dermatitis due to hypersensitivity to tobacco and enumerated other factors in the various phases in the processing and manufacturing of tobacco which may produce dermatitis. One of us (S. G.) had the opportunity over a period of twenty-five years to observe hundreds of cases of dermatoses in a cigar factory which were all traced to infections, injuries and contact with paste and other chemicals used in the manufacture of cigars rather than to hypersensitivity to tobacco. Rutledge in a discussion of Sulzberger's [4] paper on immunologic experiments on tobacco hypersensitivity stated that while he observed many cases of dermatitis in tobacco buyers and workers in factories, the patch tests have to a large extent given negative results. Schwartz and Tulipan [3] also found that patch tests with various tobacco leaves performed on a number of workers who gave a history of dermatitis failed to produce any positive reactions.

1. White, R. P.: The Dermatergoses or Occupational Affections of the Skin, ed. 4, London, H. K. Lewis & Company, Ltd., 1934.

2. Oppenheim, M.; Rille, J. H., and Ullmann, K.: Die Schädigungen der Haut durch Beruf und gewerbliche Arbeit, Leipzig, Leopold Voss, 1926, vol. 2.

3. Schwartz, L., and Tulipan, L.: Occupational Disease of the Skin, Philadelphia, Lea & Febiger, 1939.

4. Sulzberger, M. B.: Recent Immunological Studies in Hypersensitivity to Tobacco, J. A. M. A. **102**:11 (Jan. 6) 1934.

As for agricultural workers engaged on tobacco plantations, the dermatoses seen have been considered as due to the fertilizers used, i. e., phosphates, carbonates and sulfates, or to the insecticides, i. e., lead and arsenic used against insects and molds. Infestations with larva migrans and ground itch occurring in tobacco workers in tropical and subtropical countries are mentioned by White.[1] This has also been observed in some of the southern states. During the processes of curing, sweating and fermenting tobacco, dermatoses have been described in workers, but rarely has hypersensitiveness to tobacco itself been established.

Dermatitis due to the olive oil used in rolling the tobacco leaves to make them more slippery has been reported by Collis.[5]

Heller,[6] Koelsch [7] and Listengarten [8] have observed changes in the nails during the manufacturing process. These changes were brownish discolorations and thickening of the nail, breaking off of the nail plate at the free edge and subungual hyperkeratoses. Both the mechanical irritation and the chemical action of the tobacco juice were considered as contributory factors in the changes of the nails.

Blaisdell [9] described a dermatitis in cigar rollers and tobacco workers and stated that the juice of the tobacco plant will cause a most stubborn dermatitis on the fingers and palms of some people. He cited the history of a cigar roller on whose hands the eruption would clear up while he was absent from work but would recur on his return to work. The condition lasted a number of years until the patient changed his occupation.

Karrenberg [10] reported severe dermatitis caused by tobacco leaves in a 40 year old female worker in a cigaret factory. Her work consisted of separating the packed and pressed tobacco leaves. Dermatitis developed on her hands after she had worked only three or four days. A few days later there was a burning sensation on the face, followed by an acute, erythematous, vesicular, oozing eruption extending to the neck which compelled her to discontinue work. This condition would clear up while she was away from work and would recur on her return. Cutaneous tests with tobacco leaves gave strongly positive results,

5. Collis, cited by Schwartz and Tulipan.[3]

6. Heller, J., in Oppenheim, Rille and Ullmann,[2] vol. 3, p. 40.

7. Koelsch, F., cited by Heller.[6]

8. Listengarten, A. M.: Professionelle Veränderungen an den Nägeln von Tabakarbeitern, abstracted, München. med. Wchnschr. **77**:1119 (June 27) 1930.

9. Blaisdell, J. H.: Case Histories in Dermatology: Cigar Rollers and Tobacco Workers, Urol. & Cutan. Rev. **28**:664 (Nov.) 1924.

10. Karrenberg, C. L.: Zur Kasuistik der phytogenen Berufsdermatosen. Hauterkrankungen durch Tabakblätter, Dermat. Ztschr. **52**:30 (Feb.) 1928.

showing vesiculation after six to twelve hours of contact. All other cutaneous tests, with trichophytin, solution of formaldehyde, iodoform and other control substances, gave negative results.

Stauffer [11] observed on the hands and fingers of a 44 year old woman who had worked in a tobacco factory since her early youth first vesicular and then crusted rhagadiform eczema which took thirteen weeks to heal. There was a recurrence when she returned to work, at first after eighteen weeks, later after three days and then after two days. A patch test proved that she was highly sensitive to tobacco, while other substances did not cause a reaction. Dry tobacco leaf did not give any reaction, but when moistened it caused severe edema, erythema and vesiculation.

Moncorps [12] described occupational eczema in a female worker on whom all attempts to desensitize, through intracutaneous injections of a watery solution of tobacco leaf extract, were unsuccessful.

Franchi [13] observed about 60 cases of dermatitis in female workers in a cigar factory. The sites of predilection for the dermatitis were the interdigital areas, the palmar surfaces of the fingers, the palm and occasionally the lower third of the forearm and the anterior ulnar border. Infrequently an eruption was noted on other parts of the body, such as the face and the neck. He carried out extensive studies regarding the cause and found that his patients gave negative reactions to patch tests with macerated tobacco leaves and to the ingredients of the paste used in making the cigars (starch, flour and alum). However, he obtained positive results to patch tests when the paste and tobacco leaf were used together and applied near the hands. In control cases the patch tests gave negative results.

Touton [14] reviewed all the cases of tobacco dermatitis reported up to 1932 but accepted only Karrenberg's case as clinical and experimental proof of hypersensitivity due to tobacco leaves.

We have recently treated 3 cigar makers with dermatitis which after long observation and investigation proved to be due to contact with tobacco leaves, and the cases have been accepted as instances of

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11. Stauffer, H.: Ueber einen Fall von Tabakekzem, Schweiz. med. Wchnschr. **48**:1203 (Nov. 30) 1929.

12. Moncorps: Ekzema professionale bei einer Tabakarbeiterin, Zentralbl. f. Haut- u. Geschlechtskr. **30**:804, 1929.

13. Franchi, F.: Dermatite professionale delle sigaraie, Gior. ital. di dermat. e sif. **78**:475 (June) 1937.

14. Touton, K.: (*a*) Hauterkrankungen durch phanerogamische Pflanzen und ihre Producte, in Jadassohn, J.: Handbuch der Haut- und Geschlechtskrankheiten, Berlin, Julius Springer, 1932, vol. 4, pt. 1, p. 648; (*b*) Nachträge zu dem Ergebnissbericht die Hautkrankheiten durch Pflanzen und Pflanzenproducte, Zentralbl. f. Haut- u. Geschlechtskr. **20**:833, 1926; (*c*) Pseudophytogene und phytogene Berufs- und Gewerbedermatosen, Dermat. Ztschr. **49**:385 (Feb.) 1927.

occupational dermatoses by the New York State Labor Department. The scarcity of these cases and the medicolegal aspects involved with regard to compensability have prompted us to report them.

REPORT OF CASES

CASE 1.—Mrs. F. D., a white woman 49 years old, born in the United States, was first seen on Oct. 4, 1937. She complained of an itching eruption of the fingers, hands, wrists, thighs and buttocks. There was no history of any previous cutaneous disease. She had been working in a cigar factory for thirty-one years, making cigars, the last few years as a forewoman, handling and inspecting tobacco leaves and occasionally making sample cigars. About January 1937 she noticed that her fingers and hands became reddened and had a burning and itching sensation. Later the skin became dry, tight and cracked. Her condition would improve when she was absent from work but would recur on returning.

The physical examination gave negative results. The skin of the palmar and dorsal surfaces of the fingers, especially on the left hand, appeared reddened, dry, scaly, thickened and fissured, especially above the interphalangeal joints. Similar changes were present on the palms. On the flexor surfaces of the wrists the skin was thickened, lichenified and slightly pigmented. The nails were not involved. On the inner surfaces of the thighs there were reddish brown thickened dry scaly patches, diffuse, symmetrically distributed and irregularly outlined, with lichenifications at the periphery. Similar changes, with excoriations and crusts, were present on the right buttock (she had placed the moist tobacco leaves on her lap while sorting them). Patch tests made on the forearm with tobacco leaves, both with the filler and wrapper, gave strongly positive reactions, which persisted for several weeks.

The treatment consisted of the application of soothing salves and pastes and fractional doses of roentgen rays once a week. The condition did not clear up for several months, until she discontinued working in the factory.

CASE 2.—F. L., an Italian, 51 years old, has been working as a cigar maker for over thirty years. In October 1937 he noticed an eruption on both hands. He gave no history of any previous cutaneous disease. The eruption consisted mainly of vesicles, inflammatory infiltrations and fissures, accompanied by burning and itching, with a predilection for the thenar and hypothenar eminences.

A patch test made with tobacco filler gave a positive reaction. He was recalcitrant to treatment while working. His condition improved when he stopped working but relapsed when he resumed work. His condition cleared up only after a prolonged course of treatment, including fractional roentgen ray treatments, and when he gave up his work.

CASE 3.—A. D., 53 years old, Italian, had been working as a cigar maker practically all his life. A dermatitis developed in November 1936. The lesions involved both hands, especially the thumbs, and consisted of vesicles with a serous exudate, scales and fissures. He complained of itching and burning sensations.

Patch tests with wrapper tobacco and paste gave negative results. Patch tests with filler tobacco gave positive reactions, but when it was combined with the paste the reactions became strongly positive.

His condition improved or disappeared when he did not work for several days at a time, but an exacerbation of the dermatitis occurred within a few hours after his resuming work. His condition finally cleared up when he gave up his work.

INVESTIGATION

We carried out patch tests with both the wrapper and the filler tobacco leaf and obtained positive reactions to the filler in all 3 cases and to the wrapper in cases 1 and 2; in case 3 the patch test with the wrapper gave negative results. Patch tests with raw tobacco leaves, washed and unwashed, gave negative results in all 3 cases. The results of patch tests with old, dry tobacco leaves were also negative. All the positive reactions were obtained from tobacco leaves which were actually used at the time of the manufacture of the cigars at the factory. These leaves all went through the processes of curing and fermentation before they were shipped to the factory. Those used as fillers went through further processes of resweating and dampening of the wrapper, but no flavoring substances, such as vanilla, perfumes or wines, had been added. Patch tests made with the paste used in the manufacture of cigars gave negative results, but when this paste was used together with the tobacco leaf a much stronger positive reaction was obtained in 1 case than when the tobacco leaf was used alone.

Microscopic and cultural examination for fungi from cutaneous lesions of 2 patients and from the paste used gave negative results. It is interesting to note that the reaction from the patch tests persisted for several weeks, at first showing erythema and edema. Later the skin became thickened and tight, showing small raised papules; the picture was similar to the changes which occurred on the sites of the dermatitis. The same observation was made by Karrenberg,[10] who emphasized the similarity in the evolution of the reactions to patch tests and of the original dermatitis.

COMMENT

We have omitted the description of the lengthy processes involved in the planting, harvesting, curing and fermenting of tobacco which are necessary before the leaves can be utilized for the manufacture of cigars. These have been excellently described recently by Schwartz and Tulipan.[8] We shall discuss the question of individual hypersensitivity to tobacco.

Our cases showed many similarities in the history, clinical manifestations, course and recalcitrance to therapy. None of the patients gave any history of previous disease. All of them had worked in the same cigar factory for twenty-five years, using the same materials without any deleterious effects. The areas involved were the fingers, especially the thumbs, hands and forearms, the areas most exposed in making cigars, except in case 1 (in which the thighs and buttocks of a female worker were also involved, because she had placed the tobacco leaves in her lap and allowed the tobacco juice to soak through her

clothing). The onset of the eruption seemed to coincide, which suggested the possibility that the dermatitis in all 3 patients may have been caused by the same brand of tobacco (Tennessee and Kentucky). The fact that in some workers a rash would develop from foreign tobacco only while in others it would be caused by certain brands of domestic tobacco was also obtained by Schwartz and Tulipan [3] in their survey among tobacco workers.

Attempts to determine the exact nature of the irritating substances which produce the dermatitis from the tobacco leaves have not been successful. Microscopic and cultural examinations of material from the lesions and of the pastes gave negative results, which would exclude the possibility of a pseudophytogenic factor. Karrenberg [10] considered this possibility and made investigations with the extracts of various micro-organisms (bacteria, yeast and fungi) which ordinarily inhabit the tobacco leaves, but he obtained negative results using extracts prepared from cultures grown only from the tobacco leaves with which his patient worked.

It is apparent that the dermatitis in our patients was caused by recently fermented tobacco, since no case of dermatitis due to either raw tobacco leaves or dry tobacco had been observed, and none was reported in smokers due to contact with cigars. Dampened, wetted tobacco leaves, however, may produce severe dermatitis. Deacon [15] observed in an Italian soldier, who to avoid military service had put "Toscani" cigars under the axillas overnight, soaking them first for several hours in water, a diffuse erythema on the trunk and extremities, a red pharynx and a temperature of 40 C. (104 F.).

The view expressed by Schwartz and Tulipan [3] that possibly traces of insecticides on the leaves or some flavoring substances may play a role in the causation of the dermatitis could not be substantiated in our cases. One might accept the suggestion that some of the irritating chemicals produced during the process of curing and fermentation may cause the dermatitis.

The difficulty in ascertaining the exact chemical nature of plants—and the tobacco plant may be included—which produce dermatitis has been discussed by Touton,[14] Karrenberg [10] and others. They considered tobacco dermatitis as being due possibly to nitrogen-free substances which originate from the etheric oils of the glandular hair of the leaves, to nicotianine (derived from the fermentation of nicotine), to other alkaloids not free from nitrogen and even to butyric and malic acid.

The presence of nicotine cannot be considered of great importance in the causation of the dermatitis if one interprets correctly the findings

15. Deacon, N.: Poisoning by Tobacco Applied to the Skin, Brit. M. J. **2**:61 (July 10) 1926.

of Stauffer [11] and Sulzberger.[16] Stauffer [11] found that while a watery infusion of tobacco in 1:1,000 dilution gave a positive reaction, nicotine in a corresponding concentration gave a negative reaction. Sulzberger [16] in his comparative studies of the reactions to nicotine and to denicotinized tobacco extracts observed many hundred positive reactions to the tobacco and only 2 cases in which there were slight to moderate reactions to nicotine. He concluded that the reactions are caused by parts of the tobacco other than nicotine.

We were unable to confirm in our cases the observation made by Karrenberg [10] that spontaneous desensitization may occur on the fingers and hands after repeated contact with tobacco. This would be explained only by the fact that possibly other brands of tobacco may have come in contact with the skin. While 1 of our patients remained free from her dermatitis as late as the beginning of 1940, she worked as a forewoman in the factory and avoided contact with tobacco.

Attempts at desensitization by intramuscular injections of tobacco infusion carried out by Stauffer [11] have failed. Reactions to patch tests were still positive after a series of injections, and there was a recurrence of the dermatitis within one day after the patient returned to work. Moncorps [12] similarly was unsuccessful in his attempts at desensitization with infusions of tobacco.

SUMMARY AND CONCLUSIONS

Three cases of occupational dermatitis in cigar makers working in the same factory are reported.

The dermatitis was due to contact with tobacco leaves and can be attributed to acquired hypersensitivity to recently fermented tobacco leaves.

The condition in all 3 cases proved recalcitrant to all therapeutic measures and cleared up only when working with tobacco was discontinued.

While many of the dermatoses in the tobacco industry may be caused by trauma, infections, pastes and various chemicals used in the manufacture of cigars, an acquired hypersensitivity to tobacco leaves may occur and should be kept in mind.

Dr. L. Schwartz, Medical Director of the United States Public Health Service in charge of dermatoses investigations, Washington, D. C., gave valuable suggestions and aid in the preparation of this paper.

75 East Eightieth Street, New York.

390 Main Street, Danbury, Conn.

16. Sulzberger, M. B.: (*a*) Studies in Tobacco Hypersensitivity: A Comparison Between Reactions to Nicotine and to Denicotinized Tobacco Extract, J. Immunol. **24**:87 (Jan.) 1933; (*b*) Recent Immunological Experiments in Tobacco Hypersensitivity, Bull. New York Acad. Med. **9**:294 (May) 1933.

WETTING AGENTS

NEW SYNTHETIC CHEMICALS OF USE IN FINER AND MORE EFFICIENT TOPICAL DERMATOLOGIC THERAPY

WERNER W. DUEMLING, M.D.
FORT WAYNE, IND.

Studies of the permeability and absorptivity of the skin have engaged the interest of dermatologists from time to time, because since ancient days the management of most cutaneous diseases has been dependent in a large part on local and topical treatment. According to Eller and Wolff,[1] these studies have established that:

A. Medicaments applied to the unbroken skin may be absorbed into the blood stream.

B. The rate of absorption may be influenced by the vehicle as well as by the drug it contains.

C. Volatile substances such as alcohol, ether and benzine are vehicles with a much higher rate of absorption than fats.

Eller and Wolff [1] in their own studies on permeability and absorptivity of the skin came to the following conclusions:

A. Fats permeate the skin and do so in a large measure along the hair shafts and into the oil gland ducts.

B. Liquid fats permeate the skin more rapidly than solid fats.

C. Animal fats show the greatest depth of penetration, with vegetable fats next and mineral fats least.

D. Most of the fats show optimum penetration between four and six hours after application. After six hours, the quantity of fat in the deeper tissues appears to diminish.

Until a few years ago dermatologists were limited in their choice of basic materials to the animal, vegetable or mineral fats and oils. Maynard [2] called attention to the use of a synthetic saponifying agent, triethanolamine, and its possibilities in the preparation of emulsions, creams and soaps. He stated that one of the outstanding physical characteristics of this organic compound was the fact that it markedly

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Read at the Sixty-Third Annual Meeting of the American Dermatological Association, Inc., Colorado Springs, Colo., June 1, 1940.

1. Eller, J. J., and Wolff, S.: Permeability and Absorptivity of the Skin, Arch. Dermat. & Syph. **40**:900 (Dec.) 1939.

2. Maynard, M. T. R.: Triethanolamine: An Adjunct to Dermatologic Therapy, Arch. Dermat. & Syph. **25**:1041 (June) 1932; **34**:268 (Aug.) 1936.

lowers surface tension. This would bring it under the classification of surface-active agents, and although it does have some power of penetration when brought into contact with the skin, this ability is not due to lowering of the surface tension.

More recently Goodman [3] enlarged somewhat on the uses of triethanolamine and developed some basic formulas for its utilization in the preparation of emulsions, creams and soaps. He called attention to the facts that it produces no irritation of the skin and that the triethanolamine ricinoleate was found effective for detoxifying Staphylococcus aureus and gave evidence of detoxifying tubercle bacilli. Gross [4] also developed some excellent formulas for ointment bases utilizing triethanolamine in combination with stearic acid.

Triethanolamine is prepared by the action of ammonia on ethylene oxide. Commercially it contains a mixture of monoethanolamine, diethanolamine and triethanolamine in various proportions. It has a p_H of 10.6, and the triethanolamine soaps are practically neutral, having a p_H of 8.

Another modification which has been found valuable in compounding technic and in the production of more elegant emulsions and creams is the addition of cholesterol or oxycholesterol to mineral fat, which permits the incorporation of varying amounts of water to produce a water-in-oil emulsion. These are called "absorption bases," and when ammoniated mercury was added to the base it was found to have a higher antiseptic potency than the U. S. P. ointment.

A year ago Klauder, Gross and Brown,[5] in a comprehensive study of hand creams and soaps, called attention to the extensive use of sulfonated esters, ethers and alcohols in industry because of their wetting, penetrating, emulsifying or detergent properties. He stated that the addition of one of these compounds (sodium lauryl sulfate) to the sulfonated oil mixtures did not essentially improve their detergent properties.

Chemical literature indicates increasing interest in these newer organic compounds with wetting and detergent properties, the study of which has led to newer knowledge of surface chemistry.[6] A "wetting agent" is defined as a substance which, by means of its effect in lowering interfacial tension, increases the penetration and acts as a detergent or emulsifying agent or in some other way manifests surface activity. It is

3. Goodman, H.: Cosmetic Dermatology: I. Triethanolamine, Arch. Dermat. & Syph. **36**:116 (July) 1937.

4. Gross, E. R.: Ointment Bases, read at the meeting of the American Academy of Dermatology, Philadelphia, Nov. 7, 1939.

5. Klauder, J. V.; Gross, E. R., and Brown, H.: Prevention of Industrial Dermatitis, Arch. Dermat. & Syph. **41**:331 (Feb.) 1940.

6. Bartell, F. E.: Surface-Active Agents, Indust. & Engin. Chem. **31**:31 (Jan.) 1939.

known that every homogeneous substance has a surface or interface and that five different types are possible: gas-liquid, liquid-liquid, gas-solid, liquid-solid and solid-solid interfaces. The fact that over a thousand patents have been issued covering new and old compounds which have wetting, penetrating, emulsifying or detergent properties attests further the interest in these substances. As a group, the esters of sodium sulfosuccinates have been found to be the most powerful wetting agents yet described, when measured by the Draves test,[7] which measures the varying time that standard skeins of cotton yarn require to sink in different concentrations of aqueous solutions of wetting agents. The discovery of these esters of sodium sulfosuccinic acid, by Jaeger[8] in 1933, and the simple reaction of their production from maleic acid or fumaric acid not only made these powerful agents commercially available but contributed to the theory of surface-active compounds.

Wetting agents are used in the following industries:

Textile	Metal processing	Laundry
Electroplating	Lubricating	Paint
Paper	Fruit washing	Rug cleaning
Leather	Embalming	Dry cleaning
Pigment	Insecticides	Cosmetic
		Rubber

CHEMICAL STRUCTURE OF THE MOLECULE[9]

The molecule of a wetting agent is composed of hydrophobic and hydrophilic groups, giving it a dual nature and causing it to become oriented at an interface. If a minute quantity of fatty acid[10] is placed on a water surface under suitable conditions, it spreads as a monomolecular layer. A molecule of a fatty acid is composed of a long hydrophobic chain and a rather weak hydrophilic group, COOH. This structure gives it a polar-nonpolar character and places it in the class of surface-active compounds.

When the similarity in molecular structure of a fatty acid and a wetting agent is recognized, it may readily be seen that the molecules of a wetting agent on the surface of water will have a tendency to locate themselves in such a position that their hydrophilic groups are directed downward into the water while their hydrophobic groups extend above the surface. Thus the surface tension is reduced by modifying the unbalanced forces of molecular attraction at the surface of the water.

7. Am. A. Textile Chemists & Colorists, Yearbook **13**:162, 1935-1936.

8. Jaeger, A. O.: United States Patent 2,028,091, 1936.

9. Caryl, C. R., and Ericks, W. P.: Esters of Sodium Sulfosuccinic Acid, Indust. & Engin. Chem. **31**:44 (Jan.) 1939.

10. Langmuir, I.: The Shapes of Group Molecules Forming the Surface of Liquids, Proc. Nat. Acad. Sc. **3**:251, 1917.

The obvious difference between a fatty acid and a wetting agent is that the former is relatively insoluble in water while the latter is soluble.

Since soaps and primary fatty alcohol sodium sulfates have similar aliphatic structure but different solubilizing groups, they possess both

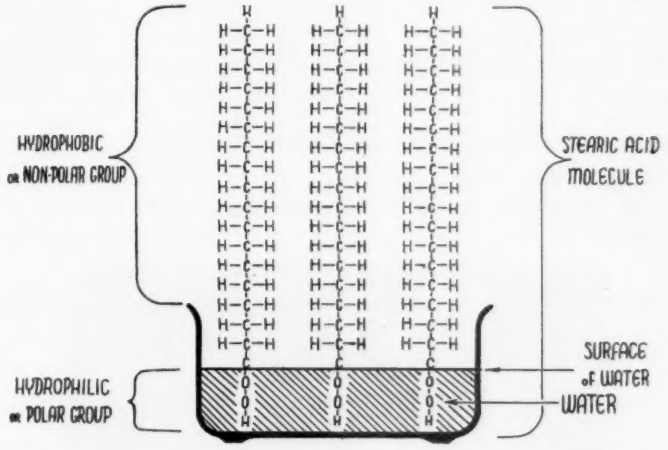


Fig. 1.—Graphic representation of stearic acid molecules on the surface of water.

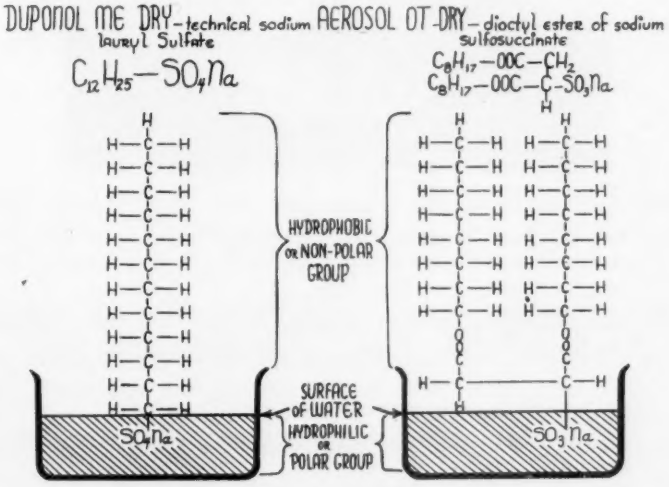


Fig. 2.—Graphic representation of molecules of wetting agents on surface of water.

similar and different properties. The emulsifying and wetting characteristics and the resistance to hard water and acids of the former are definitely inferior to those of the latter. Soaps are salts of strong bases and weak fatty acids and ionize in aqueous solutions giving an alkaline reaction.

When an attempt is made to neutralize the soap solution by the addition of an acid, part of the free fatty acid separates from the solution and the detergent properties of the soap are then greatly impaired. Inasmuch as the solubilizing group in a fatty alcohol sodium sulfate is derived from an acid of much higher strength, its aqueous solutions are practically neutral and can be acidified in the cold without visible decomposition. However, on heating, the acid solutions of a fatty alcohol sodium sulfate also decompose relatively easily. The above discussion shows that the major drawbacks of soaps as detergents have been at least partially overcome by the introduction . . . of primary fatty alcohol sodium sulfates.[9]

Compounds [9] having a chemical structure similar to that of a fatty acid may be solubilized by intensifying the hydrophilic character of the solubilizing group (neutralization with alkali and replacement of—

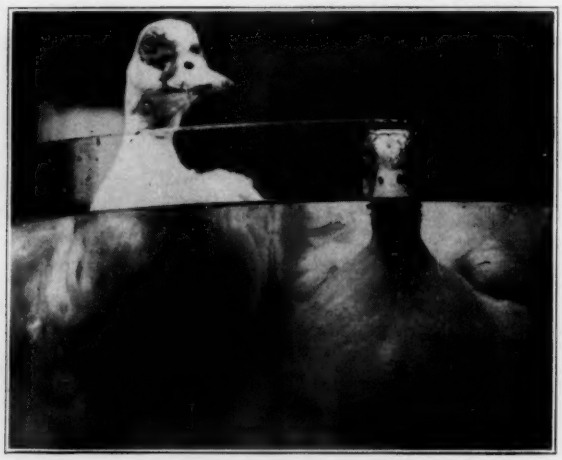


Fig. 3.—The duck on the right is unable to float in fresh water because he has been thoroughly wetted with aerosol OT (concentration not specified). The duck on the left is unwetted. (From Caryl and Ericks.[9])

COONa by—SO_4Na), by the introduction of additional solubilizing groups (sulfonation) or by shortening the hydrocarbon chain.

CLASSIFICATION OF WETTING AGENTS

From the foregoing considerations Caryl and Ericks [9] concluded:

A wetting agent should possess the following major properties:

1. High wetting power even in very low concentration.
2. Stability in dry form and in solutions, especially in acid solutions where soaps cannot be used.
3. Solubility in water and in organic solvents, especially in nonpolar solvents.
4. Resistance to hard water.

These properties can be attained by properly selecting and balancing a hydrophobic group with a hydrophilic group which is not easily hydrolized and which gives the

compound solubility in water without depriving it of its solubility in organic solvents.

Wilkes and Wickert [11] presented a classification covering most types of wetting agents, which greatly simplified this complex group of products. The following quotation is from their article:

In group A are listed the various types derived from fatty sources—specifically, soaps, fatty alcohol sulfates, and sulfated fatty acid esters and amides. The polar or water-soluble groupings in all these compounds is a primary one, located at the end of the nonpolar portion of the molecule. In contrast, group B presents the available types of the more truly synthetic surface-active compounds, including

TABLE 1.—*Classification of Wetting Agents* *

Group	Type No.	Formula †	Description	Relative Wetting Power of Each Type as Marketed, %
A	1	$R-COONa$	Soaps	
	2	$R-SO_4Na$	Fatty alcohol sulfates	23
	3	$R-CONHC_2H_4SO_4Na$	Sulfated fatty acid amides	5
	4	$R-COOC_2H_4SO_4Na$	Sulfated fatty acid esters	6
B	1	R'_2-CHSO_4Na	Secondary alcohol sulfates	25
	2	$R'-OOC-CH_2$ $R'-OOC-\underset{\displaystyle H}{\overset{\displaystyle |}{C}}-O-SO_3Na$	Sulfated esters of higher alcohols and dibasic acids	Not marketed
	3	$R'-Ar-SO_3Na$	Alkylaryl sulfonates	6
	4	$R'-OOC-CH_2$ $R'-OOC-\underset{\displaystyle H}{\overset{\displaystyle |}{C}}-SO_3Na$	Sulfonated esters of alcohols and dibasic acids	100
C			Miscellaneous	24

* From Caryl and Ericks.[9]
† R = fatty alkyl group; R′ = primary or secondary nonfatty alkyl group; Ar = aryl or aromatic group.

the secondary alcohol sulfates, sulfated esters of higher alcohols and dibasic acids, and the numerous alkyl derivatives of aryl or aromatic sulfonates. Each of these types contains its polar group in a secondary position with the nonpolar portion extending from it in two directions.

Caryl and Ericks [9] revised Wilkes' and Wickert's classification (table 1) to include wetting agents of the aerosol series as type 4 in group B.

AEROSOL WETTING AGENTS [12]

Aerosol OT dry is the trade name for the dioctyl ester of sodium sulfosuccinate in 99 to 100 per cent concentration and is the most effec-

11. Wilkes, B. G., and Wickert, J. N.: Synthetic Aliphatic Penetrants, Indust. & Engin. Chem. **29**:1234 (Nov.) 1937.

12. Aerosol Wetting Agents, New York, American Cyanamid and Chemical Corporation.

tive wetting agent, when compared with all others; its wetting power increases only slightly in acid and considerably in alkaline solutions.

Aerosol OS is an alkyl naphthalene sulfonate, practically 100 per cent pure, and is unique in that its wetting power is greatly increased in 5 per cent sulfuric acid and is more than doubled in 5 per cent sodium hydroxide.

Caryl and Ericks [9] stated:

> Factors mainly contributing to the outstanding properties of aerosol OT [dry] are its highly effective wetting power, its stability in solid form and in neutral and acid solutions, its purity (99 to 100 per cent), and its resistance to hard water and ability to disperse calcium and magnesium soaps.
>
> In alkaline solutions aerosol OT [dry], which is an ester, hydrolizes readily, and its use at p_H above 9 is not recommended. Aerosol OS has excellent wetting properties in alkaline solutions.

COSMETIC USAGE [13]

The aforementioned physical and chemical properties of the aerosol wetting agents make them excellent emulsifying assistants and give to them stability in the presence of acids and of alkalis.

Lotions.—The following formula is for a semifluid lotion which has excellent softening properties yet does not produce an oily effect:

Cetyl alcohol	2 per cent
Stearic acid	2 per cent
Liquid petrolatum	10 per cent
Aerosol OT, 10% in aqueous solution	10 per cent
Water	76 per cent

The cetyl alcohol, liquid petrolatum and stearic acid are heated until clear, and the 10 per cent aqueous solution of aerosol OT is added and well dispersed by stirring while the solution is warming. The water is brought to the temperature of the first component and added to it while it is being agitated. Too much agitation will produce foaming; therefore, agitation is stopped immediately after emulsification has taken place.

This formula may be varied in many ways by altering the proportions of the component parts.

Creams.—A typical formula for a cream is the following one:

White wax	11 per cent
Paraffin	10 per cent
Liquid petrolatum	40 per cent
Water	29 per cent
Aerosol OT 10% in aqueous solution	10 per cent

Melt the white wax and paraffin in the liquid petrolatum by heating the mixture to from 65 to 70 C. Heat the 10 per cent aqueous solution of aerosol OT dry and

13. Bergy, G. A.: New Compounds in Pharmacy Practice: Wetting Agents, Am. Professional Pharmacist **5**:18 (Jan.); 17 (Feb.); 140 (March); 430 (April); 494 (May) 1939.

the water to the same temperature and while stirring add the mixture of melted wax paraffin and liquid petrolatum.

Vanishing, cleansing and liquefying creams can be made by using aerosol OT dry in conjunction with the proper substances to produce practically any type of product desired.

Shampoos.—An excellent shampoo may be prepared with the following formula:

Aerosol OT dry 100 per cent	16.00 parts
Cetyl alcohol	5.00 parts
Liquid petrolatum	5.00 parts
Lecithin	0.75 parts
Alcohol (39 C or ethyl 15 per cent)	20.00 parts
Distilled water	53.25 parts

The aerosol OT dry, cetyl alcohol, lecithin and ethyl alcohol are mixed together and allowed to stand twelve hours. This component is warmed over a steam bath until it is melted and then stirred until it is clear. The liquid petrolatum is added slowly while the mixture is being stirred, and the distilled water is added gradually. The product should be entirely clear and fluid.

The formula must be rigidly adhered to or the product will not be clear. The ethyl alcohol is necessary in order to prevent turbidity. Cetyl alcohol and liquid petrolatum are present for the purpose of preventing a "drying" effect on the hair and scalp.

For dry hair and conditions of the scalp the following formula is of use:

Aerosol OT dry, 100 per cent	10 parts
Olive oil	90 parts

The aerosol OT dry is dissolved in the olive oil by warming to about 70 C.

The clear product which results resembles the original olive oil in appearance. When used it produces a copious lather which is dense and stable.

For excessively oily hair and conditions of the scalp the following formula is recommended:

Aerosol OT dry, 100 per cent	10 per cent
Alcohol (39 C or ethyl 15 per cent)	20 per cent
Distilled water	70 per cent

This shampoo may be made either by dissolving the aerosol OT dry in the alcohol by warming and then adding the water or by allowing the aerosol OT dry to soak in the water for twelve hours and then adding the alcohol the next morning.

All of the aforementioned products may be colored and perfumed as desired. When the shampoo products are used, first the hair should be wetted with warm water and then a sufficient amount of shampoo added to form a copious lather. After the hair has been shampooed sufficiently, the suds may be rinsed away in warm water. All of the

mixtures are nonalkaline, and because of the resistance of aerosol OT to lime or alkaline earth, none of the products will form a scum with hard water.

DUPONOL (TECHNICAL SODIUM LAURYL SULFATE) [14]

Duponol is the registered trade-mark designating certain higher aliphatic alcohol sulfates and their derivatives having wetting, detergent and softening properties. These properties are present because of their ability to reduce greatly the tension at interfaces. When the interfacial tension at the surfaces of materials such as oils, fats, waxes and other solids is lowered, they become emulsified or dispersed in the body of the liquid. Since they are highly resistant to alkaline hydrolysis, they are freely rinsible and do not leave a film of insoluble matter.

The duponol products are excellent wetting, penetrating, detergent and emulsifying agents and are manufactured in nine different forms, of which duponol ME dry, derived from technical lauryl alcohol and containing a minimum of electrolytes, is especially suitable for the preparation of emulsions and creams, as in the following formula: [15]

Spermaceti	20.0 per cent
Paraffin	10.0 per cent
Liquid petrolatum (viscosity, 80 to 90)	15.0 per cent
Cetyl alcohol	1.5 per cent
Duponol ME dry	1.0 per cent
Stenol	5.0 per cent
Distilled water	47.5 per cent

The spermaceti, paraffin, liquid petrolatum and cetyl alcohol are heated together to liquefaction. The duponol ME dry and stenol are dissolved in the water and heated to the same temperature as the fats and added to them with constant agitation to form a smooth, soft cream. The consistency can be varied by increasing or decreasing the amount of the waxes and liquid petrolatum.

This ointment base is compatible with all the acids and alkalis and with both water and oil. Without breaking down it will hold up to 50 per cent alkali, 30 per cent acid, 30 per cent water, 30 per cent oil or 20 per cent water and 10 per cent oil. It is an excellent emollient, is invisible and nonsoiling and washes off readily from the skin, hair, bed linen and clothing. It is detergent and reduces surface tension, allowing for immediate absorption and thereby increasing the efficiency of all medicaments, as well as producing a cooling effect by evaporation. It leaves only a slight film of oil on the surface of the skin and is only slightly on the alkaline side.

14. Organic Chemical Specialties, Bulletin 1a, Wilmington, Del., E. I. du Pont de Nemours & Co., Inc., 1939.

15. The finished product can be obtained from the Hickok Chemical Company, Detroit.

OCENOL KD (OLEYL ALCOHOL) [16]

Ocenol KD is the trade name for refined technical oleyl alcohol and is a bland, water-like liquid with a melting point ranging from 13 to 19 C. It is soluble in most organic solvents as well as in vegetable, animal and mineral oils, fats and waxes. It is resistant to oxidation and may supplement or substitute for castor oil, liquid petrolatum and petrolatum, because, in addition to having a lubricating and cleansing action like that of these substances, ocenol KD renders the skin soft and smooth. This improvement is reflected in the following formula for cold cream:

Ocenol KD	8.0 per cent
Yellow wax	9.0 per cent
Sodium borate	0.2 per cent
Cetyl alcohol, technical	8.0 per cent
Duponol ME dry	0.6 per cent
Liquid petrolatum	17.0 per cent
Water	57.2 per cent

Heat the ocenol KD, yellow wax, cetyl alcohol, duponol and liquid petrolatum together to the melting point. Dissolve the sodium borate in the water and heat to the same temperature as the wax mixture. Add this to the wax mixture with constant stirring until it is cool. After the mixture has congealed it can be whipped, forming a white cream.

Ocenol KD is compatible with hydrous wool fat, petrolatum, stearic acid, yellow wax, cetyl alcohol, cholesterol, lecithin and wool wax, and it may be used to supplement or substitute for such materials. Besides having cosmetic properties, ocenol KD added to the oil phase of any emulsion will increase the stability of the emulsion through finer particle size.

DETERMINATION OF PENETRATION OF FATS AND WETTING AGENTS INTO THE SKIN

The technic used for the determination of fat penetration closely follows that evolved by Eller and Wolff.[1]

Mature albino rabbits were used, the areas of skin along each side of the spine being utilized. After the hair was removed with electric clippers, the test materials were applied to the skin on one side, while corresponding areas on the other side were used as controls. All test materials were applied with an applicator; the application was followed by light finger massage, and the areas were covered with a layer of cellophane attached to the skin with collodion.

A preliminary series of specimens for biopsy were taken at fifteen minute intervals for one hour, corresponding normal portions being taken from the opposite side for each substance tested. Before the specimens were taken, the areas were cleansed with 70 per cent alcohol and immediately dried. The specimens were

16. Bulletin Organic Chemicals Department, Wilmington, Del., E. I. du Pont de Nemours & Co., Inc., 1940.

fixed for twenty to twenty-four hours in a 4 per cent solution of formaldehyde, and the sections were cut 10 to 15 microns thick with the freezing microtome, by bringing the edge of the knife first in contact with the subcutaneous tissue and cutting out through the epidermis. The knife blade was carefully wiped before each cut to avoid transferring fat from one section to another. Sudan IV was used for staining the fat tissues.

The procedure followed for staining was as follows: 1. Wash in distilled water. 2. Put in 70 per cent alcohol for two seconds. 3. Transfer to sudan IV for five minutes. 4. Float into a slide. 5. Blot and rinse with 70 per cent alcohol and

TABLE 2.—*Surface Active Agents* (of Use in Cosmetics)*

Name	Type	Industry	Manufacturer
Aerosol OT,MA,AY.....	Sulfonated esters of dicarboxylic acid	All uses	American Cyanid and Chemical Corp.
Intramine.....	Sodium salt of sulfonated lauryl and myristyl collamide	Textile, cosmetic	Synthetic Chemicals, Inc.
Phosphosol.....	Tetrapotassium pyrophosphate	All uses	Monsanto Chemical Co.
Phosphotex.....	Tetrasodium pyrophosphate	All uses	Monsanto Chemical Co.
Santomerse.....	Alkylated aryl sulfonate	All uses	Monsanto Chemical Co.
Sulfatate.....	Sulfonated hydrocarbon	Textile, paper, cosmetic, leather	Glyco Products Co., Inc.
Tensol.....	Sulfonated ether	Textile, cosmetic	Synthetic Chemicals, Inc.
Tergitol penetrant 4, 7...	Higher secondary alcohol sulfate	Textile, agricultural, rubber, latex	Carbide & Carbon Chemicals Corp.
Tergitol penetrant 08.....	Synthetic primary alcohol sulfate	Coned. soln. of alkalis, acids, salts	Carbide & Carbon Chemicals Corp.
Triton W-30.....	Sulfonated aromatic ether alcohol	Textile, cosmetic	Röhm & Haas Co.
Triton 720, 812.....	Sulfonated ether	Textile, cosmetic	Röhm & Haas Co.
Wetanol.....	Modified sulfated fatty acid ester	Textile, cosmetic, paper, leather	Glyco Products Co., Inc.
Ocenol KD.....	Technical oleyl alcohol	Textile, cosmetic, paper, leather, steel	E. I. Du Pont de Nemours & Co., Inc.
Duponol ME Dry.....	Higher aliphatic alcohol sulfates	Leather, paper, metal, cosmetic	E. I. Du Pont de Nemours & Co., Inc.

* All information in this table is from F. J. Van Antwerpen: Surface Active Agents, Indust. & Engin. Chem. **31**: 66, 1939, except that on ocenol KD and duponol ME dry.

then with distilled water. 6. Counterstain with Harris' hematoxylin (with 4 per cent acetic acid) one to nine minutes, depending on the condition of the stain. 7. Rinse off quickly with distilled water. 8. Differentiate in weak acid solution. 9. Intensify the result in weak alkali solution to produce sharp nuclear detail. More contrast can be obtained by weakly staining in the dilute eosin stain. 10. Mount in glycerin or saturated solution of dextrose.

Preliminary experiments were carried out according to this method with the following substances: 1 per cent duponol (wetting agent), 15 per cent ferric chloride in aqueous solution, 15 per cent ferric chloride in an aqueous solution of aerosol OT dry (wetting agent), 15 per cent ferric chloride in an ointment base containing wetting agents, equal parts

of hydrous wool fat, petrolatum, spermaceti and cetyl alcohol, and 5 per cent ammoniated mercury in an ointment base containing a wetting agent. Specimens for biopsy were taken every fifteen minutes for one hour, and normal untreated tissue was taken from areas directly opposite to the tested areas. Ferric chloride was used with the idea of demonstrating it in the tissues by means of the prussian blue reaction, but in all instances this was a failure due to the styptic action of the ferric chloride. However, these preliminary experiments revealed that complete penetration of the entire section had taken place with the fats and wetting agents at the end of thirty minutes. Since there is variation in the normal fat content in different places along the rabbits' backs, symmetric untreated areas were used as control specimens in each instance. All experiments were checked and found to coincide.

In the second series of experiments the following substances were applied: fats with a wetting agent (duponol), fats (hydrous wool fat, petrolatum, spermaceti and cetyl alcohol) without a wetting agent, 5 per cent ammoniated mercury in fats with a wetting agent and 5 per cent ammoniated mercury in an ointment base like that of the U. S. P. ointment (white wax, hydrous wool fat and white petrolatum).

MICROSCOPIC EXAMINATION OF TISSUES

Normal Skin.—An occasional small sphere of free fat was found about the sweat glands and hair follicles. None was found free in the fibrofatty tissues, and none was found below the base of the hair follicles.

Fats Alone.—Little variation was found in the penetration of these fat substances between the fifteen and sixty minute intervals. In these specimens all showed moderate penetration of the fat chiefly about the hair follicles to a depth just below the basal layer of the skin. The few small scattered globules of fat found in the deeper subcutaneous tissues are regarded as consistent with the normal content of this tissue.

Fats with a Wetting Agent.—The following observations were made:

A. Fifteen Minutes: The fifteen minute biopsy specimen showed remarkable penetration of the fatty substances almost to the base of the hair follicles. They appeared to use this avenue of penetration rather than to go through the skin itself. Where found, the fat appeared as relatively large conglomerations of large spheres and could not possibly be regarded as normal fat content.

B. Thirty Minutes: In the thirty minute specimen the fat had penetrated through to the base of the section, a distance of 4 mm. It was abundant throughout the entire section. While it was still present about the hair follicles, it had for the most part penetrated out into the fibrofatty tissue and, instead of being located in conglomerate masses, was more finely divided, probably owing to the presence of the wetting agent.

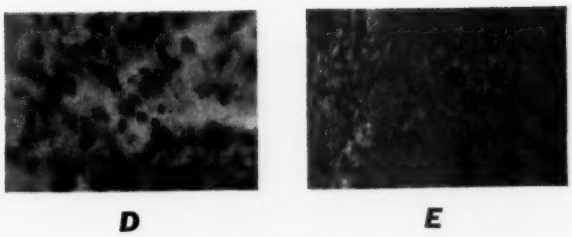
EXPLANATION OF FIGURE 4

Fig. 4.—Penetration of ointment base containing a wetting agent at fifteen minute intervals. *A*, fifteen minute specimen, showing large globules of fat (× 100). *B*, thirty minute specimen, showing deep penetration of medium-sized globules with finer division and more dispersion (× 100). *C*, forty-five minute specimen; fat has left hair follicles and is infiltrating fibrofatty tissue (× 100). *D*, forty-five minute specimen, showing the degree of dispersion (× 200). *E*, sixty minute specimen, showing fine dispersion throughout depth of section (× 200).

EXPLANATION OF FIGURE 5

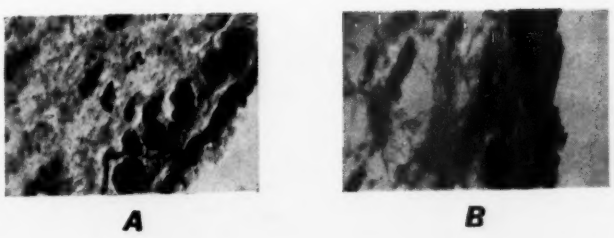
Fig. 5.—The first four pictures (*A*, *B*, *C* and *D*) show the depth and rate of penetration of the ointment base without the wetting agent. *A*, fifteen minute specimen, showing fats on the surface (× 100). *B*, thirty minute specimen, showing fats on the surface, no penetration (× 100). *C*, forty-five minute specimen, showing penetration of fat for 1.5 mm. along fair follicle (× 100). *D*, sixty minute specimen, showing penetration of fat for 2 mm. along hair follicle, with no dispersion (× 100). The next two pictures show a comparison of penetration of 5 per cent ammoniated mercury ointment with and without a wetting agent. *E*, 5 per cent ammoniated mercury in an ointment base containing a wetting agent, showing penetration of mercury (black masses) at the end of sixty minutes (× 80). *F*, 5 per cent ammoniated mercury in an ointment base (white wax, hydrous wool fat and white petrolatum), showing penetration of mercury at the end of sixty minutes.

A B C

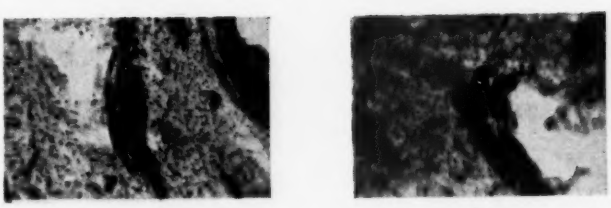


D E

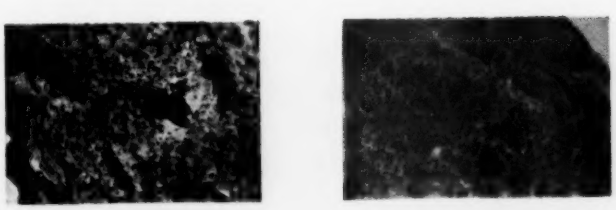
Figure 4



A B



C D



E F

Figure 5

C. Forty-Five Minutes: At forty-five minutes the fat was beginning to disappear about the basal layer of the skin and its hair follicles. It was still present in the deep portions and was even more finely divided than in the thirty minute specimen.

D. One Hour: At one hour the fat had completely disappeared from the superficial portions of the subcutaneous areas but was still present in the deepest portions of the specimen (approximately 5 mm. deep, or the entire depth of the specimen). However, it was notable that here also the fat seemed to be disappearing. It was present only in numerous tiny droplets approximately half as plentiful as in the forty-five minute specimen. This in turn was less saturated than the thirty minute specimen.

While the penetration in this experiment was much more rapid and extensive than was expected, only 2 rabbits were used, and these excellent results should be confirmed by future trials. However, it should also be stressed that the results obtained in the forty separate specimens were all consistent with their particular phase of the experiment and no discrepancies were found. It is therefore more than probable that these results can be duplicated.

Ammoniated Mercury (5 Per Cent in Ointment Base).—In fifteen minutes the ammoniated mercury was found on the surface and in the crevices of the skin, where it was combined with its ointment, which stained orange-yellow. Where the ointment had penetrated the epithelium it took the scarlet red stain. Here the surrounding hair follicles and sweat glands stained a homogeneous deep blue, so that the cell detail was difficult to make out. This was thought to be due to the action of the mercury, since it was not present in the other specimens. The difference in penetration in the fifteen, thirty, forty-five and sixty minute specimens was progressive but relatively slight. The penetration was not over 1 mm. in the sixty minute biopsy specimen. It was also noted that the fat did not disperse as it did in the aforementioned experiments.

Ammoniated Mercury (5 Per Cent) with Ointment and Wetting Solution.—The fragments of ointment remaining in the crevices of the skin stained pale blue; the fatty substances did not take the fat stain. However, wherever the ointment had penetrated the epithelium it stained as in the aforementioned experiments. The changes in the follicles and glands were similar. In the fifteen minute specimen the ointment, apparently with its content of mercury, had penetrated over one-half the length of the hair follicle, or approximately 1 mm. In the thirty, forty-five and sixty minute specimens the penetration was found to be progressive, until at the end of one hour it had penetrated the entire

specimen, or approximately 3 mm. In this experiment the fat did not tend to become divided into small particles, nor did it tend to disappear from the superficial portions or disperse through the fibrofatty tissue.

SUMMARY

Newer organic compounds, termed wetting agents, derived from the fatty alcohol sulfates, sulfated fatty acid esters and amides, from the secondary alcohol sulfates, sulfated esters of higher alcohols and dibasic acids and from the numerous alkyl derivatives of aryl or aromatic sulfonates and the esters of sodium sulfosuccinate are of value in the preparation of finer and more efficient lotions, creams and ointment bases.

Their wetting power is based on both the reduction of surface tension of the lotion, cream or ointment base and the lowering of interfacial tension between the solid and the solvent, thus permitting rapid penetration and dispersion in the solid.

This property gives to the compounds unusual emulsifying, detergent and penetrating powers, and they remain stable and effective in acid, neutral and alkaline solutions and in either hard or soft water.

They are resistant to oxidation, and they are compatible with or may supplement or substitute for the vegetable, animal or mineral fats and oils in the preparations of creams, ointments and lotions.

Dr. J. J. Hayes, attending pathologist, Fort Wayne Lutheran Hospital, assisted in the preparation of the histologic sections and photomicrographs.

Mr. R. Pantaleoni, of E. I. du Pont de Nemours & Co., Inc., Wilmington, Del., and Mr. C. R. Caryl, of the American Cyanamid Company, Stamford, Conn., supplied materials used in the experiments and made many helpful suggestions in the preparation of this paper.

ABSTRACT OF DISCUSSION

DR. EARL D. OSBORNE, Buffalo: Physicians have been much interested in these agents for several years. However, no attention has as yet been given to the employment of the sulfonated alcohols made from the higher fatty acids from the standpoint of their use in ointments, creams and lotions. This group of compounds is of such interest to dermatologists in a great many ways that I believe it behooves them to know more about them and to realize the profound effect which these compounds are bound to have on the practice of dermatology in years to come.

As Dr. Duemling has pointed out in his paper, these compounds are prepared easily and cheaply from the fatty acids. They have a great many attributes which make them of extreme value not only in cosmetics and creams and lotions of various types but in many interesting ways. They are excellent detergents. As a matter of fact, some of them are too good when considered from the standpoint of soap substitutes. Some of the sulfonated alcohols of the higher fatty acids are so good that it is impossible to use them on the hands for any length of time as a substitute for soap.

My associates and I have been doing some experimental work in preparing the sulfonated alcohols for use as substitutes for soap, and we have found that the strength can be reduced to 10 per cent or even lower. The remainder of the cake is composed of urea and nonsulfonated fatty alcohols. It is an excellent detergent, is neutral in reaction, does not have too much drying effect and is altogether an excellent preparation.

In addition to having a high quality of detergency, these compounds are in cake form, they are cheap and the smell is not obnoxious (as a matter of fact, it is not bad at all in comparison with that of soap).

These agents are also interesting from the standpoint of the leather industry. They are being used as wetting agents in treating leather preparatory to dyeing. They have the quality of allowing the dye to penetrate the leather much more rapidly than it would without their use. Since the dye penetrates more rapidly, it also comes out more rapidly under the influence of sweat and moisture in one form or another. Consequently, the use of these wetting agents is one of the reasons why there are more cases of dermatitis from dyed leather, such as that in shoes and gloves.

In the textile industry the substitution of these compounds is extremely interesting. All fabrics, including wool, silk, cotton and rayon, may be washed with these compounds. The calcium and magnesium salts of these compounds are soluble. Consequently, washing fabrics with them does not produce a precipitate of any appreciable degree in the fabric itself.

These compounds are used extensively in dentifrices of the newer types. It is an interesting thing that when compounds containing these agents were first put out they were of at least 25 per cent strength. A certain well known shampoo contained one of these compounds. Numerous cases of dermatitis from its use were reported. The manufacturers have now cut down the strength of the preparations to around 2 to 5 per cent.

As to the effect of these compounds in producing eczematization, I have made a series of patch tests in over 125 persons, with varying strengths of the compounds. The agents are really eczematizing if used in high strength.

It has been found that if the strength of the preparation used is reduced to 5 per cent or lower, the tendency to eczematization is diminished almost to the vanishing point.

I think a great deal more will be heard about the use of these agents in cosmetics and in many other ways.

DR. MARION B. SULZBERGER, New York: I agree heartily with the opinions of Dr. Duemling and Dr. Osborne that these new substances will be of increasing interest to all physicians.

About a year ago Dr. Rudolph Hecht, of Chicago, who was associated with me in New York at the time, started some experiments with these wetting agents. Aerosol OT dry was one of those used, and several others were employed. Our experiment consisted of mixing the wetting agent with substances used in routine patch tests and doing parallel patch tests with the substance plus the wetting agent and with the substance without the wetting agent. These experiments are not yet completed, and I cannot report any final results. We thought that an increased capacity of penetration might be expected and that this might make it possible, for example, to reduce the concentration of a substance materially and still get the same degree of reaction.

Thus far, it seems that the action of the wetting agent is erratic in this respect. With some compounds the peneration seems to be materially increased, while with

other compounds there does not seem to be an increase in penetration when the same wetting agent is added to the patch test solution.

I should like to point out that eventually we dermatologists shall have to be much more precise about what we want to accomplish with medicaments when we apply them to the skin. In other words, how much and how far do we really want them to penetrate? Where is the pathologic process? How deep is the change we are trying to affect with these medicaments? I believe that a great degree of penetration, or the addition of materials enhancing the powers of penetration to a great degree, may not be entirely desirable in treating many cutaneous conditions. What one attempts to accomplish with local therapy is often to obtain a more superficial action without penetration or deeper or general effects. For example, mercury is used on the surface of the skin in quantities and concentrations which could certainly not be used if all of it or even a great part of it penetrated and were absorbed through the skin. There is therefore a possibility that one may get absorption and poisoning from external, topically applied medicaments when they are incorporated in the new bases together with wetting agents, while these same substances were always previously used with impunity without the wetting agents. In other words, I think one must know how deep the medication needs to go per unit of time and per area of surface in order to achieve optimum therapeutic effects. Often only surface action or extremely superficial action is wanted and not penetration, and anything enhancing absorption may then make one shoot entirely past the mark and defeat the entire rationale and object of topical treatment.

I have reason to believe that such drugs as mercurials and phenolic derivatives, such as resorcinol and even ethylaminobenzoate, in the accustomed concentrations for topical application might become dangerous when penetration is enhanced and that this increase in penetration, with its associated added risks, would by no means necessarily be accompanied by greater therapeutic efficacy.

DR. WERNER W. DUEMLING, Fort Wayne, Ind.: As has been pointed out, these agents are being used so widely in the various industries and also in many preparations that are sold over the counter, such as cosmetics and shampoos, that one is bound to meet with some reactions, because they are definite sensitizing agents. They are also powerful emulsifying agents. Therefore, they should not be used on dry skins, because they will emulsify still further what little oil there is present. Although they are sensitizing agents, they can be used in low dilution, which will probably overcome that.

The action of these agents may seem somewhat erratic, as Dr. Sulzberger has pointed out. It may be due to the fact that in that instance the proper wetting agent has not been employed, because they do not all run true to form, and one must study the agent and know its characteristics before one attempts to use it.

The subject of the dispersion and penetration of drugs is one that cannot be overlooked. It also offers some interesting possibilities. For instance, would it be wise and could anything be gained by incorporating these agents into medication that is given intramuscularly, thus producing rapid dispersion and absorption? That has not yet been determined.

It also must be remembered that, since deeper penetration and dispersion are obtained with the use of these agents, if 1 and 2 per cent ammoniated mercury is used instead of 5 and 10 per cent, undoubtedly the same results will be obtained.

LUPUS ERYTHEMATOSUS PAPULARIS ET NODULARIS

S. IRGANG, M.D.
NEW YORK

The diverse manifestations of the acute and subacute types of lupus erythematosus are well recognized, yet the existence of the multiform features of the chronic variety have not been amply appraised. Almost a half-century ago Crocker [1] discussed some of the unusual clinical phases of chronic lupus erythematosus and described cases in which the condition simulated lichen planus and lupus vulgaris.

A diagnosis of the ordinary superficial chronic forms of this disease rarely taxes the astuteness of the dermatologist; yet its variants are difficult of perception, and reliance for diagnosis rests with the combination of histologic observations and an intimate clinical familiarity with the diverse manifestations. Also of particular microscopic significance is the noting on occasion of a tuberculoid structure, in contradistinction to the common superficial chronic types, in which this architectural configuration is rare.

The clinical phenomena of chronic lupus erythematosus vary with the intensity and points of maximum localization of the inflammatory reaction in the skin. The inflammation always affects the epidermis, and the pathologic alterations here vary primarily with the intensity of the exudative processes in the upper part of the cutis. In the superficial variety the maximum inflammatory response is usually limited to the upper third of the cutis. In the deep or tumor form the most intense reaction is observed in the lower third of the cutis and in the upper third of the subcutis. In the papular and nodular types, the variants which are mainly concerned here, the major response either may be limited to the upper half of the cutis or may involve severely this entire layer. In this type the density of the cellular infiltrate is likewise greater than in the superficial form.

Lupus erythematosus papularis et nodularis may simulate clinically rosacea-like tuberculid, lichen scrofulosorum, lupus miliaris disseminatus, sarcoid, lupus vulgaris, tertiary syphilid, lichen planus, erythema indu-

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From the Department of Dermatology and Syphilology, Harlem Hospital.

1. Crocker, H. R.: Lupus Erythematosus as an Imitator of Various Forms of Dermatitis, J. Cutan. & Genito-Urin. Dis. **12**:1 (Jan.) 1894.

ratum, papulonecrotic tuberculid, benign cystic epithelioma and basal cell epithelioma. In a review of the transactions of the various dermatologic societies it was observed that a number of likely cases of lupus erythematosus papularis et nodularis were presented with some of the aforementioned diagnoses. In a few instances a diagnosis of lupus erythematosus was offered by some of the discussers, but it was generally disregarded despite the microscopic reports, which doubtless alluded to this diseasse.

It is not possible to distinguish sarcoid from the infiltrative manifestations of this disease on clinical grounds alone. In lupus erythematosus diverse numbers of epithelioid cells may be observed singly or in aggregations. This feature may at times unduly influence the examiner to make a diagnosis of lupus vulgaris or sarcoid when the overwhelming microscopic evidence favors lupus erythematosus. I agree with Michelson,[2] who stated the opinion, "Sarcoid is being diagnosed too often from sections when the pathologic changes do not entirely conform to those accepted for sarcoid."

Sulzberger's [3] patient showed a well defined erythematopapular eruption which had been present on the face for about one and one-half years. Hypersensitivity to tuberculin was noted, but there was no tubercle formation in the sections studied (a detailed report was omitted). The eruption proved resistant to roentgen and ultraviolet radiation, in addition to intravenous injections of a gold preparation and to many topical applications, but it responded favorably to tuberculin therapy after prolonged use. The presenter considered rosacea-like tuberculid as the most probable diagnosis because of the eruption's resistance to routine treatment for rosacea and also because of a positive Moro reaction. The possibility of lupus erythematosus nodularis should be considered in this instance, for the absence of tuberculoid architecture, the cardinal diagnostic feature of rosacea-like tuberculid,[4] apparently eliminates the diagnosis of the latter disease. In my limited experience the vast majority of patients with papular or nodular manifestations of lupus erythematosus are hyperallergic to tuberculin. The additional presence of a positive Moro reaction may be expected in view of the belief that these cutaneous alterations result from tuberculous infection. The absence of a tuberculoid structure surely does not rule out lupus erythematosus.

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2. Michelson, H. E., in discussion on Sweitzer, S. E.: Sarcoid of Cheek, Arch. Dermat. & Syph. **40**:1070 (Dec.) 1939.

3. Sulzberger, M. B.: Rosacea-Like Tuberculid of Lewandowsky? Arch. Dermat. & Syph. **31**:759 (May) 1935.

4. MacKee, G. M., and Sulzberger, M. B.: Rosacea-Like Tuberculid of Lewandowsky, Arch. Dermat. & Syph. **31**:159 (Feb.) 1935.

Furthermore, some patients with lupus erythematosus are notoriously resistant to aurotherapy but respond favorably to tuberculin therapy after prolonged use.

In some instances it may be almost impossible to differentiate lupus vulgaris from lupus erythematosus nodularis on clinical grounds alone. The latter disease is frequently characterized by pinkish red lesions which show minute yellowish discolorations on diascopic pressure. Furthermore, the intensification of the eruption on exposure to sunlight, as in Gibans'[5] case, should further support a diagnosis of this disease. According to Highman,[6] the yellowish tint of these lesions of lupus erythematosus results from clumping of the fibers of elastic tissue. Gibans' patient was presented with a questionable diagnosis of lupus vulgaris erythematodes, but the discussers were unanimous in favoring lupus erythematosus.

Chronic disseminate lupus erythematosus may be mistaken for lichen planus. In fact, the clinical similarity may be so great that a histologic diagnosis of lupus erythematosus may seem incredulous.[7] Weidman[8] stated: "The histologic picture of disseminate lupus erythematosus may resemble that of lichen planus. . . . The lesions could clinically appear to be lichen planus and might show the histologic changes of lichen planus, but they are really the disseminated lesions of lupus erythematosus." In other words, these two diseases may be indistinguishable from both a clinical and a histologic standpoint, the correct diagnosis being attained only after prolonged observation, due respect being accorded the history and the benefits of therapy. The simultaneous appearance of lupus erythematosus and lichen planus in a patient, while possible, is unlikely. Feldman's[9] case is pertinent in this respect. In a man aged 47 an eruption developed on the face, upper extremities and mouth shortly after exposure to the sun. The facial lesions were considered lupus erythematosus, but the symmetric lichenoid violaceous patches on the forearms were diagnosed lichen planus. In the discussion which followed the entire eruption was considered lupus erythematosus.

It is obvious that chronic lupus erythematosus with its papular and nodular formations may simulate a variety of diseases. The condition in case 1 resembled a tertiary syphilid.

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5. Gibans, M. J.: A Case for Diagnosis (Lupus Vulgaris Erythematodes?), Arch. Dermat. & Syph. **23**:171 (Jan.) 1931.

6. Highman, W. J., in discussion on Gibans.[5]

7. Astrachan, G. D.: Lupus Erythematosus in a Patient with Lichen Planus, Arch. Dermat. & Syph. **37**:1082 (June) 1938.

8. Weidman, F. D., in discussion on Zugerman, I.: Lupus Erythematosus, Arch. Dermat. & Syph. **41**:980 (May) 1940.

9. Feldman, S.: Lupus Erythematosus and Lichen Planus, Arch. Dermat. & Syph. **26**:198 (July) 1932.

REPORT OF CASES

CASE 1.—A married Negress aged 27, a native of Texas, had been a resident of New York for two years previous to admission. The familial history was noncontributory. During childhood she had had measles, rubella and mumps, from which she had recovered uneventfully.

About ten years before admission she first experienced headaches and dizziness which appeared intermittently, especially during the early morning hours, and at times they were so intense as to induce vomiting. These complaints were treated symptomatically with indifferent results. About one year previous to admission the patient first received treatment for gonorrheal endocervicitis and salpingitis.

The cutaneous lesions first developed about two years previous to admission. At another clinic a tentative diagnosis of tertiary syphilid was made in view of the clinical characteristics and the presence of a strongly positive Wassermann reaction of the blood. Eleven weekly intramuscular injections of a suspension of bismuth subsalicylate caused great systemic improvement, including complete relief from cephalalgia and vertigo but with no apparent effect on the eruption. She then received an intravenous injection of 0.3 Gm. of neoarsphenamine, which provoked a widespread pruritic dermatitis. It became more intense one week later after an intravenous injection of 10 mg. of mapharsen.

Concomitant with the arsphenamine complication three well defined areas of alopecia of the scalp developed suddenly, two on the occipital and one on the frontal region.

With the advent of these complications the patient sought relief at the dermatologic clinic of Harlem Hospital. She was concerned chiefly with the roughly circular, well defined, pinkish red patch of slightly pruritic dermatitis on the left side of the chin because it had resisted all forms of therapy for the past two years. It was 9/16 inch (1.4 cm.) long and 5/8 inch (1.6 cm.) wide and consisted of tiny closely aggregated acuminate yellowish papules ranging in size from that of a pinpoint to that of a pinhead. A deep pinkish red flush which covered the whole area almost entirely obscured the yellowish tint of the lesions. From the summits of some of the larger lesions there were observed minute upright, flattened dark brown keratotic projections, removal of which left minute patent orifices. Resolution of the central lesions and of a few on the left border resulted in pitted scarring, which produced a honeycombed appearance. Several yellowish papules were seen embedded in these minute depressions. A few satellite papules surrounded this patch of dermatitis. Similar lesions of recent origin were scattered over the right side of the chin, but there was no evidence of grouping here. A small circular aggregation of discrete pinhead-sized, slightly scaly reddish papules was noticed on the upper lip just above the left angle of the mouth. These lesions likewise assumed a light yellowish tint with diascopic pressure. A few discrete tiny yellowish noninflammatory papules were detected on the alae nasi. There were no oral lesions. Well defined areas of alopecia on the scalp developed during arsphenamine therapy. In the occipital area the right patch was 1 inch (2.5 cm.) long and 1½ (3.8 cm.) inches wide, while the left one was 1½ by 1¾ inches (3.8 by 4.5 cm.). These areas were completely devoid of hair, moderately pruritic, erythematous and slightly scaly. The patch on the frontal border of the scalp was similar in appearance but about the size of a 5 cent piece. Arsphenamine hypersensitivity resulted in a diffuse and symmetric mild pruritic erythematous eruption on the thighs, lower part of the abdomen, trunk and eyelids. The results of the rest of the physical examination were normal except for a few carious teeth and chronic bilateral salpingitis, which appeared to be in a state of acute activity.

A hemogram showed moderate secondary anemia (hemoglobin 65 per cent and red blood cells 3,350,000). The urine was normal, and a roentgenogram of the chest showed no abnormalities. The Wassermann reaction of the blood was reported as negative. The systolic blood pressure was 120 and the diastolic 70. An intracutaneous injection of 0.1 cc. of old tuberculin in a dilution of 1 to 1,000,000 elicited a mild positive reaction.

A specimen for biopsy was taken from the circinate lesion on the left side of the chin. Resolution of the arsphenamine dermatitis was effected completely within two weeks with the aid of intravenous injections of sodium thiosulfate and local soothing applications. Intracutaneous injections of old tuberculin and the intravenous administration of gold sodium thiosulfate were then employed in an attempt to affect a cure of the lupus erythematosus. Tuberculin was administered in doses of 0.1 cc. at intervals of one to two weeks depending on the degree of local reaction. The initial dilution was 1 to 1,000,000, but this hyperergy to tuberculoprotein subsided rapidly within two and one-half weeks, for at this time a dilution of 1 to 1,000 was required to induce a satisfactory local response. Aurotherapy was administered at weekly intervals. The initial dose of gold sodium thiosulfate was 20 mg., but it was increased rapidly to 50 mg. This combined thera-

Fig. 1 (case 1).—Lupus erythematosus papularis simulating a tertiary syphilid. Pitted atrophy is evident. The eruption proved extremely resistant to aurotherapy but responded slowly to treatment with bismuth subsalicylate and tuberculin.

peutic attack proved ineffective, for five weeks later new facial lesions continued to appear and in addition there appeared on the entire anterior portion of the chest an asymptomatic discrete pinkish macular eruption and on the medial aspect of the left arm a linear area of asymptomatic, discrete, pinkish red, papular dermatitis. The original eruption on the left side of the chin became deep pinkish red; the lesions were now arranged in a serpiginous manner and partial resolution at the border was followed by a contiguous formation of new lesions. The recent developments on the anterior part of the chest and on the left arm were considered manifestations of lupus erythematosus and not evidence of an allergic reaction to gold, for they were asymptomatic and were not aggravated by continued aurotherapy. At this point treatment with gold sodium thiosulfate was discarded in favor of weekly intramuscular injections of bismuth subsalicylate in doses of 1.5 cc., and tuberculin therapy was continued. This change proved beneficial, for within one week the entire eruption showed evidence of resolution, and it continued to resolve at a slow pace when the patient was last seen at the fourth injection of bismuth subsalicylate. The dermatitis in the areas of alopecia continued to subside gradually but had not disappeared entirely at the termination of treatment. There was evidence of neither regrowth of hair nor atrophy three

months after onset of the defluvium. Interruption of treatment was necessitated because of a change of residence to another state.

The epidermis and the cutis were affected in their entirety by the pathologic process. The epidermis was irregular in contour, and normal areas were interposed between atrophic and hypertrophic alterations. The stratum corneum showed relative and absolute hyperkeratosis, the latter being limited to the underlying acanthotic prickle and granular cell layers. Minute round keratotic masses could occasionally be seen wedged into a slightly dilated follicular orifice. The granular layer varied in thickness from a double row to many layers of cells, the latter forming an integral part of the limited areas of epidermal hypertrophy. Proliferation of the stratum spinosum was restricted to definite small areas, and these lay adjacent to a normal stratum on the one hand and an atrophic layer of cells on the other. Spongiosis was evident, particularly in the hyperplastic zones. An occasional granular cell and some of the prickle cells were edematous, and a few of the latter were in a state of vacuolar degeneration. A few basal cells showed obvious liquefaction necrosis. Well defined nodes of cellular infiltration, both perivascular and perifollicular, permeated the entire cutis. In the papillae they were limited principally to overlying zones of epidermal hypertrophy; a few wandering cells could be seen invading the lower epidermal stratums. In the lower half of the cutis the infiltrate was more compact, and its borders were more sharply outlined. The small lymphocyte was the chief type of cell. In the upper part of the cutis a rare eosinophilic leukocyte could be seen at the periphery of these lymphocytic deposits, but of particular importance were the small numbers of epithelioid cells which formed a part of the cellular infiltrates in the deeper parts of the cutis. In one area a central cluster of these cells presented a picture suggestive of a "dressed" tubercle, but the small lymphocytes were so numerous as almost to obscure this tubercle-like formation.

The cutis was moderately edematous. The serous exudate was more prominent in the deeper portions and was particularly evident in the perivascular tissues and about the infiltrating cells. In a single instance the serum appeared to divide a dense cellular deposit into smaller components which lay in an edematous degenerating stroma.

A variable connective tissue reaction was seen throughout but was most intense about the appendages and zones of cellular infiltration. In one area in the papilla there was almost complete fibrous replacement of a lymphocytic nodule, and in a single area in the midportion of the cutis the fibrous tissue reaction about the coil glands was so intense as to disorganize them completely. These destroyed appendages simulated Langhans' giant cells.

The blood vessels throughout the cutis were distinctly dilated. Some of the capillary walls were edematous, and their lining endothelial cells were swollen. The wall of a single vessel in the deep part of the cutis was hyperplastic and was invaded by a few lymphocytes. The vessels of the subcutis were congested, and in the upper part of this layer an occasional narrow perivascular collar of lymphocytes was noted. A few chromatophores laden with slight deposits of melanin were seen scattered through the upper part of the cutis.

The lesions of lupus erythematosus papularis et nodularis are mainly discrete. At times there may be a tendency toward grouping, but the lesions rarely fuse. When capillary congestion is intense, diascopic pressure is necessary to visualize the yellowish color of the individual

lesions. On the other hand, this yellowish tint may or may not be present, depending on the extent of fragmentation and clumping of the elastic tissue fibers. In the event of severe focal damage to the supportive tissues, pitted scarring may be anticipated. This sequela, when it does occur, is of diagnostic significance.

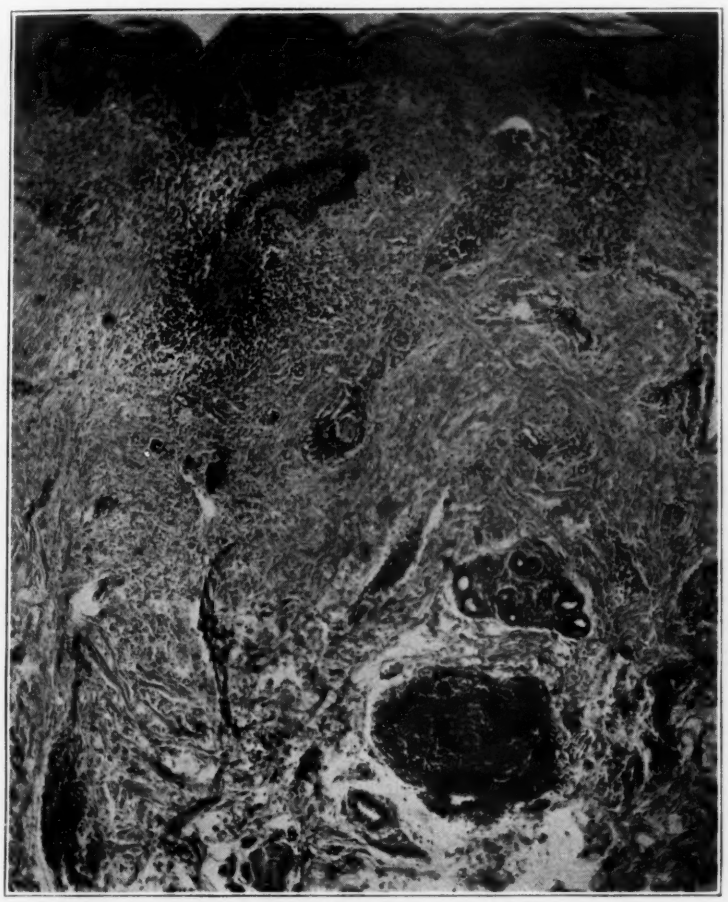

Fig. 2 (case 1).—The entire cutis is affected (low power). Some of the basal cells of the epidermis have undergone liquefaction necrosis. The perivascular infiltrate is more intense and more compact in the deeper areas. Note the thickened vessel wall in the deep part of the cutis.

The circumscribed patches of alopecia of the scalp in case 1 may be of controversial nature as regards its causation. It is considered to have the same causation as the lesions of lupus erythematosus and is not regarded as a complication of arsphenamine therapy, despite its

appearance shortly after the onset of the cutaneous complication. In my experience the partial or total defluvium which occurs subsequent to an arsphenamine dermatitis is diffuse and involves the entire scalp. Furthermore, in this instance the arsphenamine dermatitis resolved completely within two weeks, yet the dermatitis within these circumscribed areas of alopecia had not disappeared entirely three months after its

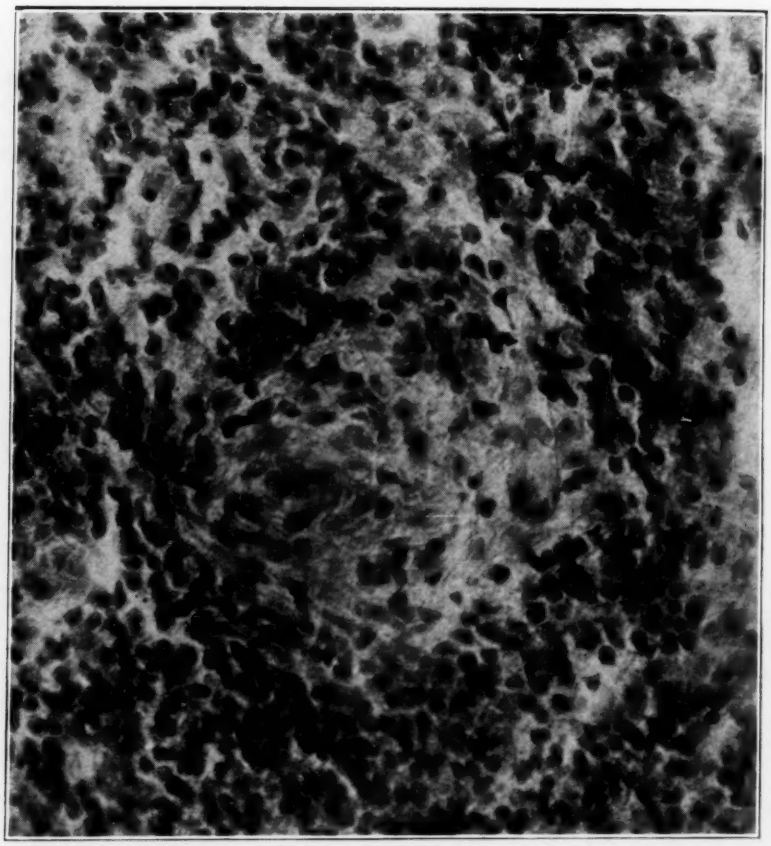

Fig. 3 (case 1).—High power photomicrograph of the deeply stained compact cellular node in the deep part of the cutis. The circular cluster of epithelioid cells surrounded by great numbers of small lymphocytes suggests an intensely inflammatory type of lupus vulgaris.

inception. Moreover, evidence of growth of hair should have been detected within this interval if the defluvium had resulted from arsphenamine hypersensitivity. To reiterate, two types of lesions evolved in the same person; the papular eruption on the face preceded the development of the ordinary superficial form on the scalp and chest and the papular

lesions on the left arm. In the latter three locations the eruption was precipitated by the abnormal reaction to the arsphenamines, while the facial lesions appeared to be reactivated by it.

The rapid subsidence of tuberculin hyperergy is unique. It was necessary to employ a concentration of 1 to 1,000, when two and one-half weeks previously a dilution of 1 to 1,000,000 was sufficient for therapeutic purposes.

The similarity of lupus erythematosus nodularis to lupus miliaris disseminatus may be so precise as to make clinical recognition most difficult. A diagnosis of the latter is made frequently despite the lack of supportive histologic evidence and despite the presence of hyperergy to tuberculin. Traub's [10] presentation is germane to the issue. A woman aged 24 had a facial eruption for six years. It consisted of small discrete papules which on resolution left pitted scars. A test with tuberculin in a dilution of 1 to 1,000,000 gave a positive reaction. The presence of a few epithelioid cells and an occasional giant cell in addition to a tremendous lymphocytic infiltration provoked conflicting microscopic diagnoses. In my experience the occurrence of a tuberculoid structure in lupus erythematosus nodularis is not rare, and the additional presence of great numbers of small lymphocytes favors this diagnosis in preference to lupus vulgaris and lupus miliaris disseminatus. That the latter two diseases are most resistant to treatment is well known. The infiltrative forms of lupus erythematosus, on the other hand, unquestionably are more amenable to therapeutic attack.

The following case suggested the possibility of either lupus miliaris disseminatus or miliary sarcoid when the patient first came under observation, but the reaction to tuberculin, the microscopic picture and the results of treatment excluded them from further consideration.

CASE 2.—A married Negress aged 39, born in Virginia, had been a resident of New York since the age of 7 years. The familial history was irrelevant. She had the usual childhood diseases, from which she recovered without known complications. The patient stated that she had not contracted either tuberculosis or syphilis. About one month prior to admission an asymptomatic eruption appeared on the face, and it continued to spread slowly until the lesions almost completely covered this area. The patient felt well and sought relief for cosmetic reasons alone.

The eruption was symmetric and nonpruritic and consisted of discrete pinkish papules and nodules which varied in size from that of a pinhead to that of a split pea. It affected chiefly the central and lateral regions of the face. An occasional lesion was seen on the vermilion border of the lower lip. The ear, the neck and the skin over the manubrium sterni were also affected, and in the last region the lesions tended to group. The eruption was unquestionably discrete, but on the left side of the nose the fusion of a few lesions produced two small linear configurations. Neither scales nor keratotic plugs were observed. Crusting and

10. Traub, E. F.: Lupus Miliaris Disseminatus Faciei, Arch. Dermat. & Syph. **40**:1042 (Dec.) 1939.

ulceration were likewise absent. A conspicuous pinkish flush over the affected areas was impressive and weighed heavily in favor of a diagnosis of lupus erythematosus. There were no oral lesions. Discrete and fused red fleshy nodules were also seen on the bulbar conjunctiva. They were arranged symmetrically in a single-band-like fashion extending outward from the corneal rim. The tonsillar crypts were infected.

The systolic blood pressure was 190 and the diastolic 124. The urine was normal. A Kahn test of the blood gave a 4 plus result. A hemogram showed mild secondary anemia and lymphocytosis (52 per cent lymphocytes). An intracutaneous injection of 0.1 cc. of old tuberculin in a dilution of 1 to 1,000,000 resulted in a positive reaction, which persisted for one week. A roentgenogram

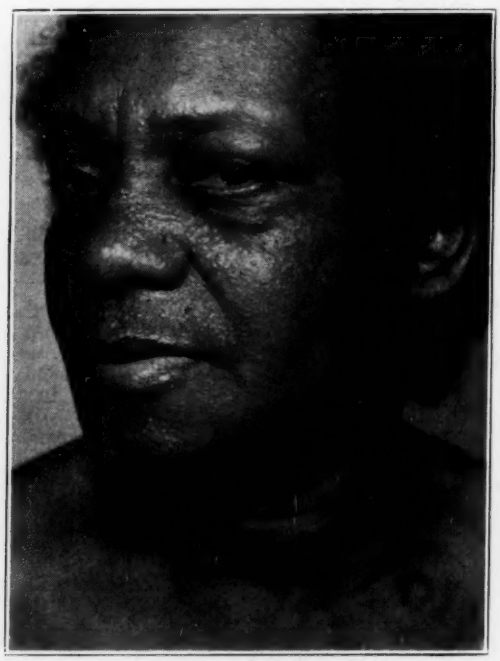

Fig. 4 (case 2).—Lupus erythematosus papularis et nodularis simulating lupus miliaris disseminatus and miliary sarcoid. Note the linear lesion on the left side of the nose and the presence of the eruption over the sternum. Similar lesions were present on the bulbar conjunctivas. The entire eruption yielded promptly to bismuth and tuberculin therapy.

of the chest showed fibrotic deposits extending from the right hilar region upward. Thickening of the interlobar pleura of the right lung and enlargement of the right hilar nodes were also noted.

Therapy consisted of six weekly intramuscular injections of a suspension of bismuth subsalicylate in doses of 1.5 cc. for the first two treatments and of 2 cc. for the remaining four. Six intracutaneous injections of old tuberculin were administered at weekly intervals in 0.1 cc. amounts. An initial dilution of 1 to 1,000,000 was employed, but later a 1 to 100,000 dilution was required to induce a

proper local response. Ferrous sulfate and brewers' yeast were also prescribed. Slight objective improvement was noted at the end of one week, but five weeks later it was readily apparent. Many of the facial lesions had disappeared without residual atrophic areas, and the conjunctival eruption was resolving rapidly. Since the patient discontinued attendance the ultimate outcome is unknown.

The massed cellular deposits in the upper two fifths of the cutis produced a marked thinning of the epidermis with complete obliteration of the papillae and

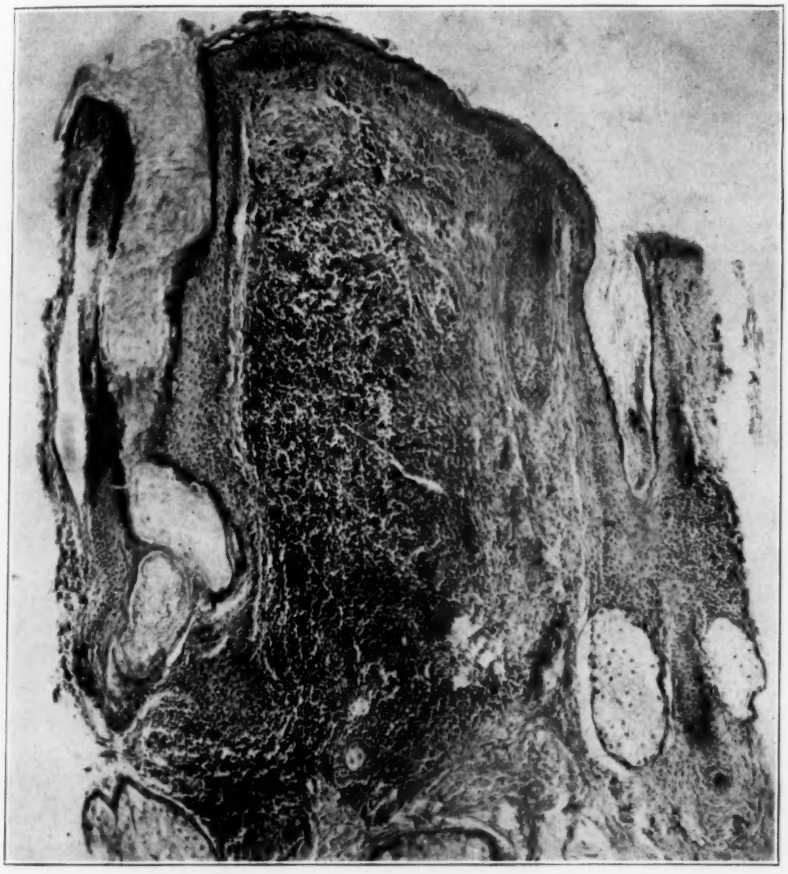

Fig. 5 (case 2).—Section of tissue from a facial lesion (low power). The dense infiltrate is limited to the upper two fifths of the cutis. The pilosebaceous follicles are widely dilated and filled with keratin.

interpapillary pegs. There was slight thickening of the stratum corneum. The intensely dilated follicular spaces were completely filled with loosely lamellated layers of keratin. The stratum granulosum was represented by a single row of flattened cells. Many cells of the atrophic stratum spinosum were edematous. Some of the basal cells likewise showed this edematous feature. There was slight interstitial edema throughout the epidermis.

The dense cellular infiltrate, both perivascular and perifollicular, was fairly well defined and was composed principally of small lymphocytes resting on an edematous collagenous framework. The edema was slight outside these cellular deposits. To a small extent the infiltrate was also composed of epithelioid cells which could be seen singly, in bands and in small circular clusters. An occasional plasma cell and a rare eosinophilic leukocyte was also observed. A connective tissue reaction was noted at the periphery of this massed infiltrate.

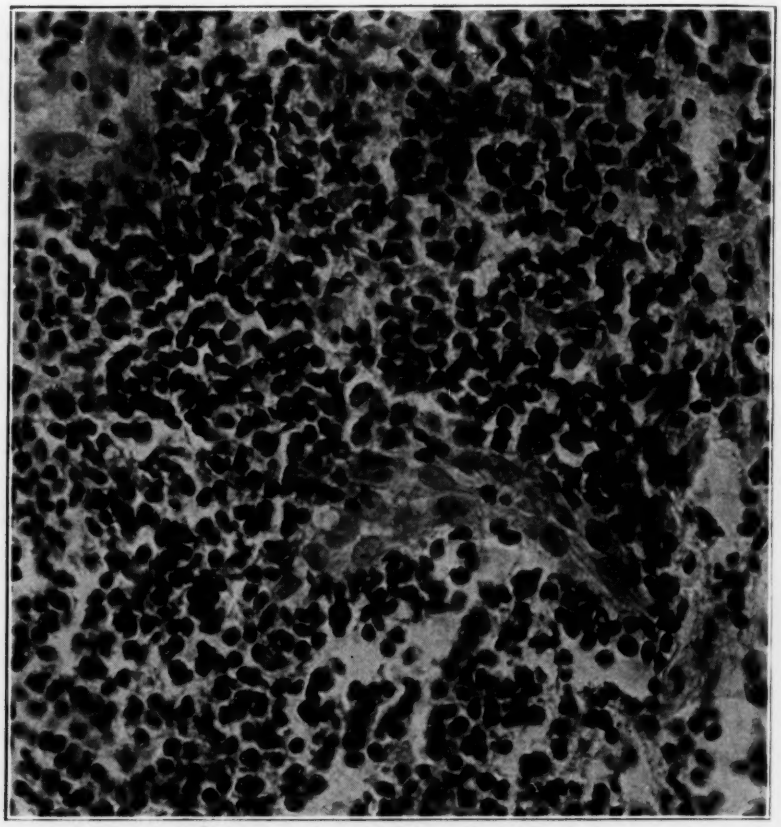

Fig. 6 (case 2).—Perivascular infiltration of epithelioid cells surrounded by dense masses of small lymphocytes (high power). The character of the infiltrate suggests the possibility of tuberculous infection.

The capillaries and lymph spaces were moderately dilated. Chromatophores were scattered through the upper one fourth of the cutis, and at rare intervals these cells were observed in the infiltrate. The dermal appendages were well preserved. There was no inflammation either in the deep part of the cutis or in the subcutis.

The presence of a significant erythematous flush over the affected area is an important clinical feature of the papular and nodular forms of lupus erythematosus. In case 2 the favorable therapeutic results and

the hyperergic response to tuberculin ruled out lupus miliaris disseminatus. Furthermore, the microscopic observations eliminated not only the latter disease but also miliary sarcoid as diagnostic possibilities.

When these unusual forms of lupus erythematosus involve the extremities they simulate clinically both papulonecrotic tuberculid and erythema induratum, although the latter two diseases can be excluded by prolonged observation alone since necrotic processes are never noted

Fig. 7 (case 3.—Lupus erythematosus papularis et nodularis simulating papulonecrotic tuberculid and erythema induratum. Crusting and ulceration were never observed during the entire course of the disease. The eruption responded well to mapharsen and tuberculin therapy.

in lupus erythematosus, regardless of type. The following report deals with such an example.

Case 3.—A married Negress aged 27, born in South Carolina, was one of 12 siblings, all of whom were living and well. She was a resident of New York for seven years previous to admission. There was no familial history of either tuberculosis or syphilis. During childhood she was ill with measles and pertussis

but recovered completely in both instances. She was in apparent good health until October 1936, when an asymptomatic eruption appeared on both legs. The patient sought relief at the dermatologic clinic of Harlem Hospital about five months after its onset. At this time a symmetric nodular eruption was observed, and since it resembled superficially a papulonecrotic tuberculid, aurotherapy was instituted. The result of a Kahn test of the blood was reported as negative, and a roentgenogram of the chest showed no abnormalities.

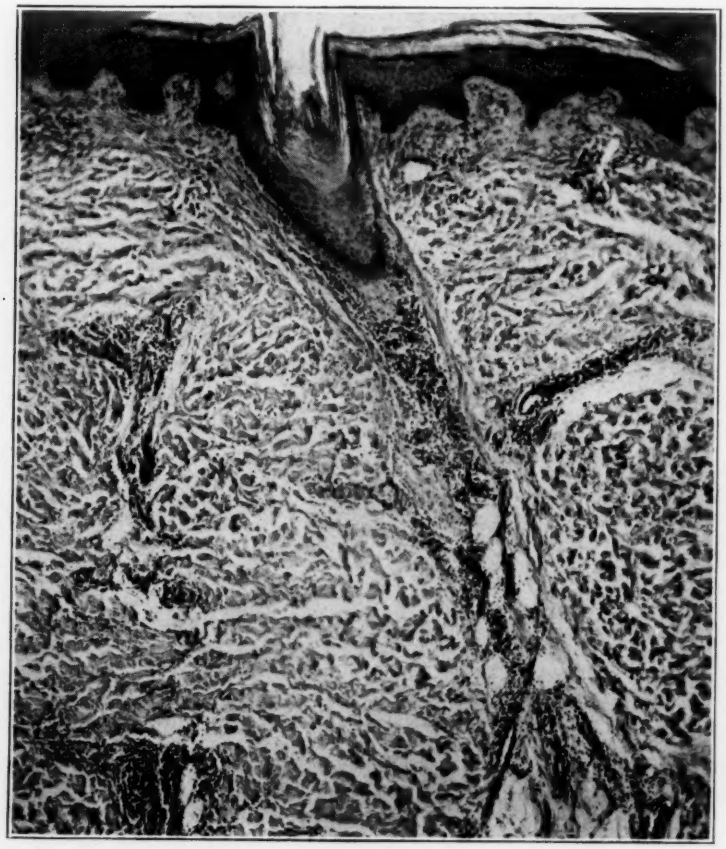

Fig. 8 (case 3).—The inflammatory reaction involves the entire cutis and the adjoining fringes of the subcutis (low power). The cellular infiltrate, both perivascular and perifollicular, is more evident in the deeper zones. Note the keratotic mass plugging the dilated follicular orifice.

The patient received six weekly intravenous injections of gold sodium thiosulfate, of 10 mg. each, with favorable results. A suspension of bismuth subsalicylate was then injected in doses of 1.5 cc. at weekly intervals, but shortly after the sixth treatment mild stomatitis was noted. After its subsidence aurotherapy was again instituted, with good effect, for after the tenth injection, each dose being 20 mg., the lesions disappeared.

From this time until one and one-half months prior to her second admission, on April 18, 1940, she remained in apparent good health and was free of cutaneous lesions. Atrophy or scarring as a sequela from the previous eruption was not noted. The recurrent eruption was exactly the same in appearance and location as the preceding one. The lesions were asymptomatic and symmetric and were observed chiefly on the extensor surfaces. The papules and nodules were pinkish red, smooth and nonscaly and varied in size from that of a pinhead to that of a split pea with a few slightly larger. Some of the earlier lesions assumed a

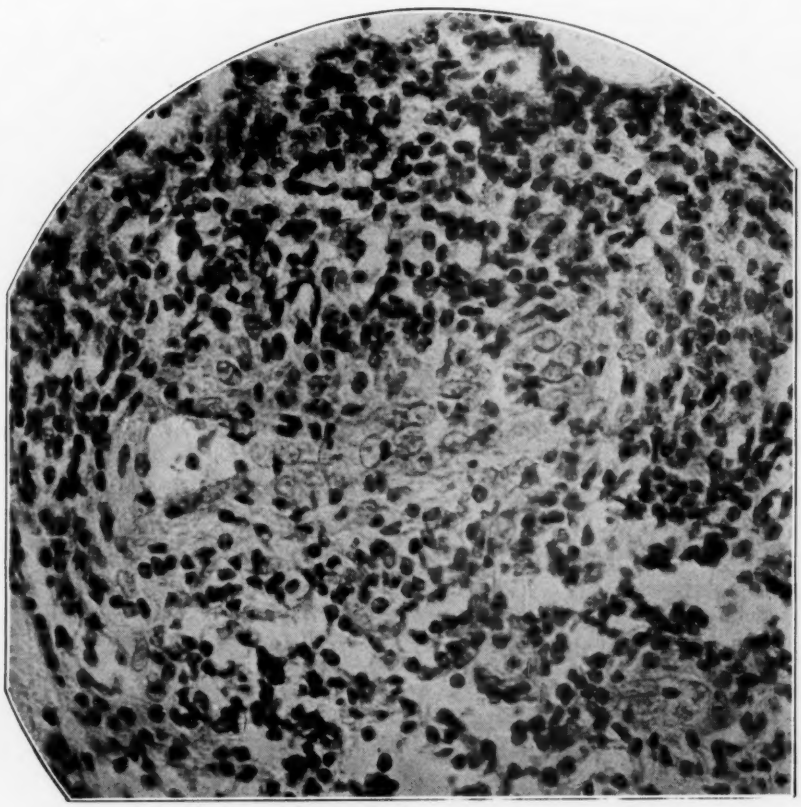

Fig. 9 (case 3).—High power photomicrograph of a perivascular node of infiltrate in the deep part of the cutis showing tuberculoid structure.

brownish tint, and their centers showed a distinct depression. A few nodules had a central or slightly eccentric flat or slightly elevated minute brownish black plug. Crusting or ulceration was not noted. The results of the rest of the physical examination were essentially normal.

The result of a Kahn test of the blood was reported as 3 plus. A hemogram showed mild leukocytosis and lymphocytosis (11,900 leukocytes and 52 per cent lymphocytes). The urinary sediment showed an occasional finely granular cast. A roentgenogram of the chest was normal. An intracutaneous injection of 0.05 cc.

of old tuberculin in a dilution of 1 to 1,000,000,000 elicited a positive reaction. The systolic blood pressure was 110 and the diastolic 82.

Therapy consisted of ten weekly intravenous injections of mapharsen, each dose being 40 mg., biweekly intracutaneous injections of old tuberculin and the administration of brewers' yeast. Sufficient tuberculin was injected to elicit a split-pea-sized local reaction. This was accomplished at first with 0.05 cc. of a 1 to 1,000,000,000 dilution, but later 0.1 cc. of a 1 to 1,000,000 dilution was required. Five weeks after treatment was commenced improvement was conspicuous, and at

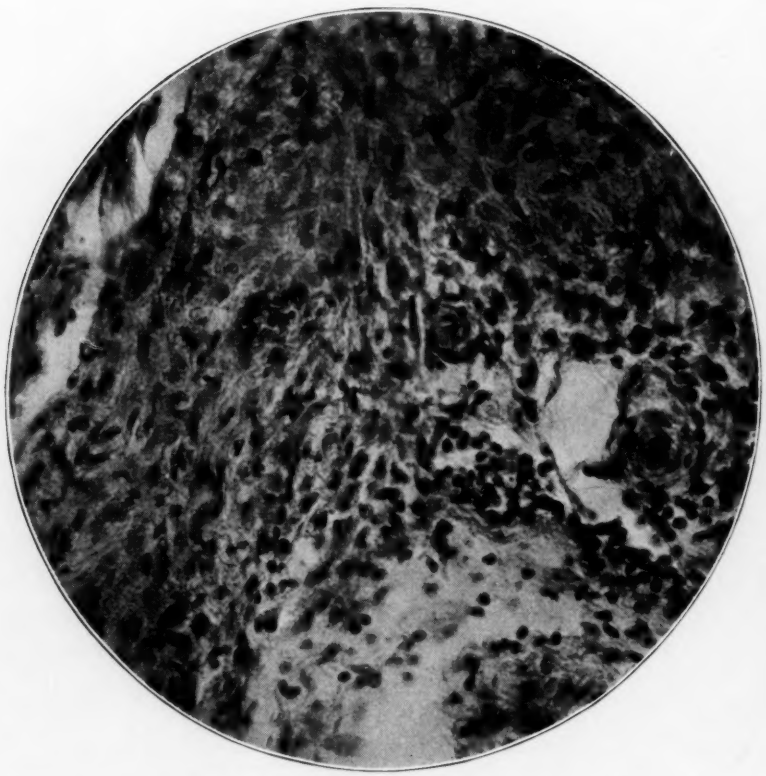

Fig. 10 (case 3).—Massed perivascular infiltration of epithelioid cells in the deep part of the cutis producing a sarcoid-like structure (high power). Note the absence of nodule formation. No giant cells were found either in this section or in any of the others from cases 1 and 2.

the end of nine weeks the eruption had resolved completely, leaving pigmentation but no residual atrophy. The patient did not return to the hospital for further observation.

The whole skin was affected. The epidermis showed moderate variation in thickness; in addition to normal areas, mild atrophic and mild hypertrophic zones were noted. There was moderate hyperkeratosis with keratotic plugging of the slightly dilated follicular and sweat duct orifices. The granular layer was normal. The

prickle cells were irregularly acanthotic, the hypertrophic changes being limited principally to the rete pegs. In some localities the rete pegs were effaced, while in others the stratum spinosum appeared normal. Slight interstitial edema was evident in this layer, and in addition an occasional prickle cell was edematous. There was no liquefaction necrosis of the basal cells. The blood vessels and lymphatics of the entire cutis were widely dilated. The capillary walls were edematous, and a few wandering cells could be seen within them. The lining endothelial cells were swollen and in a state of proliferation.

Moderate edema was evident throughout the cutis, but it was more intense about the blood vessels and appendages. The cellular exudate permeated all parts of the cutis but invaded only slightly the adjoining fringes of the subcutis. The infiltrate was most intense and most compact in the deep part of the cutis, and it lay in an edematous stroma. The small lymphocyte formed the most significant part of the infiltrate. Epithelioid cells were noted in the lower part of the cutis. They were arranged perivascularly in a single diffuse but well defined mass, in short narrow bands and in round clusters. The former resembled a "naked" tubercle and simulated sarcoid, but nodule formation was lacking. The latter two forms were surrounded by numerous lymphocytes and resembled "dressed" tubercles. Giant cells were not observed. A connective tissue reaction about the cellular deposits was comparatively slight.

Undoubtedly in a certain proportion of cases of lupus erythematosus the condition is caused by the tubercle bacillus.[11] I believe this etiologic factor especially applicable to the papular, nodular and tumor varieties. In case 3 the hyperergic response to tuberculin and the presence of definite tuberculoid structure tend to support the tuberculous concept. Patients with lupus erythematosus who show a decided hypersensitivity to tuberculin usually respond favorably to tuberculin therapy.

In case 3 papulonecrotic tuberculid can be excluded since there was neither clinical nor microscopic evidence of necrosis. The absence of atrophy or scarring likewise eliminates it from consideration. In a minority of instances the lesions of erythema induratum may resolve spontaneously without necrosis or sequelae, but this is not likely to occur in two separate attacks. Furthermore, the predominance of asymptomatic lesions on the extensor surfaces, the comparatively rapid therapeutic response and the trivial involvement of the subcutis further mitigate a diagnosis of erythema induratum.

COMMENT

Both papular and nodular forms of lupus erythematosus are not as rare as one might suspect. In the 3 cases under discussion and in 2 others observed recently the serologic reactions for syphilis were strongly positive. All 5 patients were women. I doubt whether syphilitic infection has any influence on the development of these lesions. I believe

11. Jadassohn, J.: Die allgemeine Pathologie der Tuberkulide, Wien. med. Wchnschr. **64**:36, 1914.

the infiltrative types of lupus erythematosus result from tuberculous infection; hence the hyperergic response to tuberculin, the presence on occasion of tuberculoid structure and the favorable results with tuberculin therapy are not unexpected findings. These variants may be more frequent in the Negro probably because of the greater incidence of tuberculous infection. Not all forms of chronic lupus erythematosus respond satisfactorily to treatment with bismuth and gold preparations. Tuberculin therapy should be utilized in patients who display a high degree of sensitivity to this bacterial extract.

SUMMARY

Lupus erythematosus papularis et nodularis is not rare. This variant may simulate many other diseases. Three cases are discussed; the condition in 1 resembled a teritiary syphilid, in another lupus miliaris disseminatus and miliary sarcoid and in the third papulonecrotic tuberculid and erythema induratum.

The infiltrative types may appear simultaneously with or independent of the superficial forms. The clinical phenomena of lupus erythematosus vary with the intensity and points of maximum localization of the inflammatory exudate in the skin.

The lesions of the papular and nodular types have an erythematous appearance, and while they have a tendency to group, the lesions rarely fuse. They may resolve without residual atrophy. The pitted scarring, when it does occur, is characteristic.

These variants of chronic lupus erythematosus are considered to result from tuberculous infection. This belief is substantiated by the following facts: These patients are unduly sensitive to tuberculin; they react favorably to tuberculin therapy, and a tuberculoid structure is not an uncommon finding.

All 3 patients in this series were women, and all had syphilitic infection. In 1 case the condition proved extremely resistant to treatment, while in the other 2 it reacted well to injections of tuberculin, in addition to bismuth therapy in 1 and the administration of mapharsen in the other.

The photomicrographs were furnished by the Department of Pathology, Harlem Hospital.

TOILET SOAPS, SOAP SUBSTITUTES AND HARD WATER

A STUDY OF VARIOUS COMBINATIONS BY PATCH TESTS

HOWARD J. PARKHURST, M.D.
TOLEDO, OHIO

A complete factory for the manufacture of soap, about 1,700 years old, was discovered in the excavations at Pompeii. The Romans had learned the art of soap making from the Gauls, who may have gotten it from the Phoenicians.[1] For centuries soaps were crude and costly, and perfumes were more generally used, but now the soap industry has developed to such a point that a number of excellent toilet soaps are available even to those in the poorest circumstances. The value of soap and water in personal hygiene, as an aid in preventing the spread of disease and in the treatment of various cutaneous disorders, need scarcely be mentioned. The surgeon relies on soap and running water to help free his hands of bacteria before he operates, and many investigators have testified to its efficiency.[2] In 1920 Norton [3] reached the conclusion that ordinary toilet soaps are at least as effective in this way as the so-called germicidal soaps and therefore the latter may be considered superfluous.

Most dermatologists advise against the use of soap in certain cutaneous conditions. Beauty parlors do much to discourage the use of toilet soaps and to popularize the substitution of cleansing creams. There are large numbers of women who take pride in the belief that soaps do not agree with their skin and who boast that no soap has touched their face for years.[4] Fortunately, they continue to use soap on the rest of the body and generally do not complain of irritation.

Read at the Sixty-Third Meeting of the American Dermatological Association, Inc., Colorado Springs, Colo., June 1, 1940.

1. Simmons, W. H.: Soap (Its Composition, Manufacture and Properties), London, Sir Isaac Pitman & Sons, Ltd., 1933, p. 1.

2. Walker, J. E.: Germicidal Properties of Soap, J. Infect. Dis. **38**:101, 1926; abstracted, J. A. M. A. **86**:395 (May 1) 1926; The Germicidal and Therapeutic Applications of Soaps, ibid. **97**:19 (July 4) 1931. Price, P. B.: Bacteriology of Normal Skin: New Quantitative Test Applied to a Study of Bacterial Flora and Disinfectant Action of Mechanical Cleansing, J. Infect. Dis. **63**:225, 1938; abstracted, J. A. M. A. **112**:181 (Jan. 14) 1939.

3. Norton, J. F.: Soaps in Relation to Their Use for Hand Washing, J. A. M. A. **75**:302 (July 31) 1920.

4. Fox, H.: Debunking Cosmetics, Hygeia **18**:300 (April) 1940.

For twenty years I have been looking in vain for a person who actually could not tolerate a properly selected, ordinary, good toilet soap when used with the proper technic. Furthermore, I have yet to see anything but benefit from the proper use of such a soap, even in conditions in which it is generally considered to be contraindicated.

There are many cases of dermatitis due to contact with strong laundry soaps, in which the condition usually clears up when milder soaps are substituted. Especially in the colder seasons dryness, chapping and irritation of the skin have been ascribed to the use of toilet soaps, and investigators have stated the belief that the free alkali has deprived the skin of its protecting natural oil and thus decreased its resistance to various sensitizing agents or potential local irritants.[5] Dermatologists are familiar with the observations of authors concerning changes in the p_H of the cutaneous surface after the use of soaps and the buffer action of the normal secretions in returning the p_H to normal point.[6] I am inclined to agree with Jordon, Walker and Osborne[7] and others that the alkali is probably not an irritant but that it prepares the skin for irritation by various external agents, including perfumes in the soaps themselves. There has been a search for soap substitutes, and the use of sulfonated oils and alcohols is increasing,[8] although these substances may also act as irritants in certain cases.[8a]

There is a prevalent feeling that hard water combined with toilet soap is irritating to the skin. I have conducted a few experiments to investigate this question. In the first place, hard water may be defined as water which contains in solution bicarbonates or sulfates of calcium and magnesium. The carbonate, which may be thrown down by boiling, gives "temporary hardness," while the sulfate is not affected by boiling and gives "permanent hardness." (Calcium hydroxide [slaked lime] will remove "temporary hardness"; sodium carbonate will remove "permanent hardness."[9]) It is interesting to note that when hard water is heated carbonates alone are precipitated as a fine powder, but any

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5. (*a*) Hansen, P.: Einige Untersuchungen über die Einwirkung der Seife auf die Haut, Acta dermat.-venereol. **17**:589, 1936. (*b*) Bonnevie, P., in discussion on Hansen.[5a]

6. Sharlit, H., and Scheer, M.: The Hydrogen-Ion Concentration of the Surface of the Healthy Intact Skin, Arch. Dermat. & Syph. **7**:592 (May) 1923.

7. Jordon, J. W.; Walker, H. L., and Osborne, E. D.: Studies in the Eczematizing Properties of Soaps, New York State J. Med. **36**:791, 1936.

8. (*a*) Blank, I. H.: Action of Soap on Skin, Arch. Dermat. & Syph. **39**:811 (May) 1939. (*b*) Klauder, J. V.; Gross, E. R., and Brown, H.: Prevention of Industrial Dermatitis, with Reference to Protective Hand Creams, Soap and the Harmful Role of Some Cleansing Agents, ibid. **41**:331 (Feb.) 1940.

9. Smith, A.: General Chemistry for Colleges, New York, Century Company, 1911, p. 392.

sulfates which are present may be attracted and brought down mechanically with the carbonates, forming a film or scale which adheres to the sides of the container.[10]

Soap is made by combining fats or oils with solutions of caustic alkalis. The reaction may be illustrated as follows:

$$(C_{17}H_{35}.COO)_3C_3H_5 + 3\ NaOH \rightarrow C_3H_5(OH)_3 + 3\ C_{17}H_{35}.COONa$$

glyceryl stearate — glycerin — sodium stearate (soap)

Most soaps, excepting those of potassium and sodium, are insoluble (or only slightly soluble) in water. Very small quantities of potassium or sodium soaps will produce suds in pure water. But if they are added to hard water, an insoluble curd of calcium and/or magnesium soaps is precipitated. Approximately the following reaction takes place:

$$Ca(HCO_3)_2 + 2\ C_{17}H_{35}.COONa \rightarrow 2\ NaHCO_3 + (C_{17}H_{35}.COO)_2Ca,$$

temporary hardness — soluble soap — insoluble calcium soap (precipitated)

and

$$MgSO_4 + 2\ C_{17}H_{35}.COONa \rightarrow Na_2SO_4 + (C_{17}H_{35}.COO)_2Mg$$

permanent hardness — soluble soap — insoluble magnesium soap (precipitated)

All of the calcium and magnesium salts in solution must be precipitated in this manner before any of the soluble sodium (or potassium) soap will be free to form a lather and be used for cleansing purposes.[10] With the use of a standard soap solution, this reaction is commonly employed for the quantitative determination of the degree of hardness of a given water.[11] In the laundry these insoluble calcium and magnesium soaps are attracted to the washed goods and are hard to dislodge from the fabric. It is stated that new shirts contain 0.5 to 3 per cent ash, while old ones yield 7 to 9 per cent, a convincing difference.[12] Evidently these precipitated calcium and magnesium soaps adsorb a variable amount of sodium soap, and one might expect this to act as an irritant of the skin.[13] Simmons [14] stated:

> All soaps are much more readily soluble in hot than in cold water, and while in hot water the solutions are generally clear, in cold water they are slightly turbid, due to hydrolysis (i. e., decomposition of the soap by water into free caustic alkali and an acid soap). This decomposition increases (to a certain point) with the amount of water added, and varies according to the nature of the fatty acids of the soap.

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10. Friend, J. N., and Twiss, D. F.: Oxygen, in Friend, J. N.: Textbook of Inorganic Chemistry, Philadelphia, J. B. Lippincott Company, 1924, vol. 7, pt. 1, pp. 236-240.

11. Standard Methods for the Examination of Water and Sewage, ed. 8, New York, American Public Health Association, 1936, pp. 59-62.

12. Stanislaus, I. V. S., and Meerbott, P. B.: American Soap Maker's Guide, New York, Henry Carey Baird & Company, 1928, p. 66.

13. Mason, W. P.: Examination of Water, Chemical and Bacteriological, New York, John Wiley & Sons, Inc., 1931, pp. 37-39.

14. Simmons,[1] p. 102.

This formation of acid soaps on standing must be remembered when one considers the amount of precipitate obtained when soap is added to distilled water and the mixture is allowed to cool and stand. Blank [8a] has shown, by means of patch tests, that fatty acids are primary irritants, this tendency being in inverse proportion to the molecular weight and in direct ratio to the degree of alkalinity of the cutaneous surface.

Excepting the two superfatted ones, the soaps used in the present experiments were common low-priced products purchased at the grocery. They included a popular hard water castile soap rich in coconut oil, an abrasive soap containing a considerable amount of pumice, a 5 cent cake of shaving soap, a common olive oil soap and six of the largest-selling toilet soaps, one of which contains a phenolic compound as a prominent ingredient. A fresh cake of each soap was grated into fine particles, and these were accurately weighed in 1 Gm. lots. A sulfonated oil which is

TABLE 1.—*Analyses of Waters Used in Experiments*

(Grains per Gallon)	Toledo Tap Water (Maumee River)	Michigan Tap Water (Deep Well)	Other Ohio Water (Deep Well)
Total solids	22.2	24.8	36.503
Silica	0.4	0.7	0.752
Iron and aluminum oxides	0.1	0.1	2.162
Calcium carbonate	3.9	9.8	7.170
Calcium sulfate	9.0	4.0	13.586
Magnesium carbonate	4.1	5.4	0
Magnesium sulfate	0	0	9.453
Sodium chloride	...	...	2.273
Potassium chloride	...	...	1.107

commonly recommended and a popular sulfonated alcohol sold as a non-oily shampoo were measured in lots of 1 cc.

Toledo tap water is fairly hard. Its analysis appears in table 1. The amount of ordinary toilet soap required for an average seven minute bath, using a wash cloth, with 30 gallons (114 liters) of Toledo water at a temperature of 103 F. (39.4 C.) was estimated by accurately weighing the cake of soap before and after use. The amount used in each of three such baths was found to be 12.95, 14.2 and 16.6 Gm., respectively, an average of 14.58 Gm. of this particular soap per bath. Two harder waters from deep wells, one supplying a town in southern Michigan and the other used in northwestern Ohio, were used also in the experiments. Distilled water was employed as a control.

In these investigations an attempt was made, as far as possible, to duplicate conditions found in the actual daily home use of toilet soaps. When such a soap is used, it is applied to the wet skin directly or in the form of a concentrated lather, and after variable amounts of rinsing with either fresh or soapy water the skin is more or less thoroughly dried. Unless the rinsing has been thorough, with plenty of soapless

water, a residue would be expected to remain on the skin. In the present experiments this residue or precipitate was obtained in considerable amounts and used for patch tests.

In the first series of experiments, recorded in table 2, 1 Gm. of each soap, or 1 cc. of each liquid soap substitute, was added to 1 liter each of Toledo, Michigan and distilled water at a temperature of 103 F. (39.4 C.), this being accepted as an ordinary temperature for a warm

TABLE 2.—*Experiments with Soaps and Waters; Amount of Precipitate Formed in Grams and Results of Patch Tests with Precipitates*

Hard Water	Distilled Water	Toledo Tap Water (October 1939)	Toledo Tap Water (March 1940)	Michigan Tap Water (March 1940)
Castile soap	0.003	.....	0.620	0.398
Patch tests	Negative	.....	Negative	Negative
Toilet soap 1	0.221	0.813	0.770	0.792
Patch tests	Negative	Negative (1S)*	Negative	Negative
Toilet soap 2	0.201	0.746	0.768	0.750
Patch tests	Negative	Negative (1S)	Negative (1S)	Negative
Toilet soap 3	0.061	0.740	0.776	0.685
Patch tests	Negative	Negative (1S)	Negative (1S)	Negative
Toilet soap 4	0.190	0.761	0.804	0.509
Patch tests	Negative	Negative (1S)	Negative (1S)	Negative (1S)
Toilet soap 5	0.150	0.648	0.584	0.840
Patch tests	Negative	Negative	Negative	Negative (1S)
Toilet soap 6	0.005	0.590	0.793	0.790
Patch tests	Negative	Negative	Negative	Negative
Abrasive soap	0.256	0.670	0.772	0.784
Patch tests	Negative	Negative (1S)	Negative	Negative (1S)
Shaving cake	0.200	0.740	0.829	0.794
Patch tests	Negative	Negative (1S)	Negative (1S)	Negative
Olive oil soap	0.362	0.751	0.809	0.842
Patch tests	Negative	Negative (1S)	Negative (1S)	Negative (2S)
Superfatted soap 1	0.335	0.746	0.726	0.700
Patch tests	Negative	Negative (2S)	Negative (3S)	Negative (2S)
Superfatted soap 2	0.305	0.753	0.721	0.601
Patch tests	Negative	Negative (1S)	Negative	Negative (3S)
Average weight of precipitates		0.7207	0.7476	0.707
Sulfonated oil	0	.....	0.073	0.325
Patch tests	Negative	.....	Negative (2S)	Negative (1S)
Sulfonated alcohol	0	.....	0.028	0.173
Patch tests	Negative	.....	Negative (1S)	Negative (1S)

* "S" means "slight erythema lasting less than forty-eight hours"; the numeral preceding it designates the number giving this reaction.

bath. The mixtures were shaken thoroughly for ten minutes and allowed to stand for at least twenty-four hours at temperatures varying from 60 to 68 F. (33.3 to 37.77 C.). Generally, with the hard waters, an immediate flocculent precipitate was formed in the soap mixtures. After standing for one or more days, these mixtures were shaken and passed through a suction filter. The precipitates were weighed and used for patch tests on 32 normal persons between the ages of 19 and 46 years, most of the subjects being student nurses. The weights of these precipitates are only approximately accurate, because small portions were unavoidably lost in the process of filtration, but they should suffice for practical purposes when average amounts are being considered.

Authorities consider shaving soap in cake form to be a fine and nonirritating product. Stanislaus and Meerbott [15] stated: "The essential in shaving preparations is that they must be absolutely neutral, produce a creamy lasting lather, be nonirritant, softening the beard without smarting, and leave the skin with a cool and pleasant feeling." Therefore it was felt that cake shaving soap might well be used, as a last resort, for an inexpensive mild substitute in any case in which there might be irritation from other soaps. So additional experiments were conducted with such a soap, and the results are shown in table 3. One gram, finely divided, was added to a liter of cold water (60 to 68 F. [33.3 to 37.77 C.]) and also to a liter of warm water (103 F. [39.4 C.]). Five-tenths gram of the soap was added to a liter of warm water.

TABLE 3.—*Experiments with Shaving Soap and Waters*

	Weight of Precipitate in Grams	Results of Patch Tests
With 1 Gm. of soap:		
Cold distilled water	0.386	Negative (3E)*
Cold Toledo tap water	0.823	Negative (1S)
Cold Michigan water	0.830	Negative (2S)
Cold Ohio well water	0.880	Negative (2S)
Warm distilled water	0.005	Negative (1S)
Warm Toledo tap water	0.722	Negative (2S)
Warm Michigan water	0.803	Negative (2S)
Warm Ohio well water	0.835	Negative (1S)
With 0.5 Gm. of soap:		
Warm distilled water	0.003	Negative
Warm Toledo tap water	0.465	Negative
Warm Michigan water	0.423	Negative (1S)
Warm Ohio well water	0.351	Negative

* "E" means "moderate erythema lasting seventy-two hours"; "S" means "slight erythema lasting less than forty-eight hours"; the numeral preceding the letter designates the number giving that reaction.

Toledo, Michigan and Ohio well water and distilled water were used. Each mixture was shaken for ten minutes and filtered at once, without being allowed to stand, and the precipitates thus obtained were weighed and used for patch tests of the same 32 normal subjects.

The precipitates listed in table 3 have been analyzed by Dr. D. J. Kooyman.[16] The results are summarized in table 4, and his report is as follows:

A sample of the material was taken from the filter and washed with warm water to remove the soluble sodium soap. The insoluble material was ashed. The ash was weighed and taken up in hydrochloric acid, and the amount of calcium in the ash was determined. The amount of magnesium was found by difference. The precipitates from cold water contained some soluble soaps. Those from warm water were practically all calcium and magnesium soaps. The agreement between the precipitates from the same waters is not particularly good, but I believe the

15. Stanislaus and Meerbott,[12] p. 503.

16. Kooyman, D. J.: Personal communication to the author.

total amount of hard water soap parallels the total hardness of the waters. The amounts of calcium and magnesium soaps in the precipitates do not correspond with the quantities present in the waters, since the magnesium soaps are from two to three times as soluble as the calcium soaps.

COMMENT

As the tables indicate, the three hard waters contained both calcium and magnesium salts in solution and showed different degrees of temporary and permanent hardness. It will be noted that the amount of precipitate is large, that it is a little greater in cold than in warm water and that it does not increase if the mixture is allowed to stand. When 0.5 Gm. of soap was used, approximately half as much precipitate was

TABLE 4.—*Analyses of Precipitates from Table 3*

Precipitate Examined (Shaving Soap plus Water)	Weight of Precipitate, Gm.	Amount Insoluble in Warm Water per Cent	Amount of Ash in Precipitate, per Cent	Amount of Calcium Oxide in Precipitate, per Cent	Amount of Magnesium Oxide in Precipitate, per Cent
Cold distilled water	0.386	0	0	0	0
Cold Toledo tap water	0.823	47.0	8.92	73.2	26.8
Cold Michigan water	0.830	56.0	9.03	80.0	20.0
Cold Ohio well water	0.880	75.6	10.20	83.2	16.8
Warm distilled water	0.005	0	0	0	0
Warm Toledo tap water	0.722	52.0	10.46	93.2	6.8
Warm Michigan water	0.803	81.3	9.42	79.2	20.8
Warm Ohio well water	0.835	97.8	10.07	92.8	7.2
Warm distilled water	0.003	0	0	0	0
Warm Toledo tap water	0.465	97.0	10.00	86.8	13.2
Warm Michigan water	0.423	97.0	10.40	89.5	10.5
Warm Ohio well water	0.351	94.3	10.30	87.6	12.4

obtained. With the harder waters the amount of precipitate was no greater, on the average, than with Toledo water. This is explained as follows:[16]

One gram of soap really contains about 0.85 Gm. of actual soap, since there is approximately 15 per cent moisture in soap as purchased. Since the equivalent weight of sodium is 23 and that of calcium is 20, the hard water precipitate will have nearly the same weight as the original soap. Therefore, if 0.85 Gm. of dry precipitate is obtained, it means simply that all of the soap has precipitated out. The precipitate could then be no heavier no matter how hard the water, unless enough soap had been added to combine with all of the calcium and magnesium salts which were in solution.

When distilled water was used a moderate precipitate appeared on standing at a cool temperature. Acid soaps probably formed a part of this precipitate, which was practically absent in the case of a popular floating soap and a hard water castile soap. It was greater in an abrasive hand soap, probably due to a deposit of pumice, and greater still with

two superfatted soaps and one popular olive oil soap, the last three soaps producing an oily residue on the filter paper. Sulfonated oil left no precipitate in distilled water, but there was a small amount of oily precipitate when Toledo water was used and a considerable amount with Michigan water. Sulfonated alcohol, containing no oil, behaved similarly, but the deposit in hard waters was the least of all.

Twenty-four hour patch tests with all of these hard water precipitates on 32 normal subjects (also observed after forty-eight and seventy-two hours) gave negative results, except for an occasional slight erythema, which soon faded. All of the results were considered to be negative, for I agree with Jordon, Walker and Osborne [7] that "mild erythema without papules or vesicles should not be regarded as a positive finding." In 4 cases there was a fairly pronounced erythema, with no vesicles or edema, lasting seventy-two hours, following the application of the precipitate from shaving soap and cold distilled water which had been filtered at once. This was attributed to the presence of undissolved soap particles in the cold water, and Kooyman has verified this.[16] It was noted that about 25 per cent of the 32 subjects reacted with a more or less pronounced erythema to the application of waterproof adhesive tape. But the important fact is that none of the hard water precipitates, with soap or soap substitutes, appeared to be sufficiently irritating to the normal skin to give a positive result in a patch test.

PRACTICAL APPLICATIONS

Especially in the winter, when the skin is deficient in natural oil, soaps and hard water are often blamed for dryness, chapping and irritation of the skin. This chapping seems to occur more readily after the repeated use of hard water castile soap, and therefore such soaps should be avoided if possible. It has been shown that toilet soaps rob the skin of oil, but in view of the beneficial effects, their use must be considered essential for proper hygiene. The use of superfatted or olive oil soaps which leave an oily residue even in distilled water does not seem advisable. One can choose from a number of excellent toilet soaps on sale in every grocery, and, as Hansen [5a] and Bonnevie [5b] have pointed out, there is little danger of irritation with the use of a proper washing technic. A bland oil may be applied to the clean skin after washing if the skin tends to chap.

My experience with soap substitutes is limited, but thus far it has been disappointing. In a case of mild seborrhea capitis, for example, itching seemed to recur much sooner after a shampoo with sulfonated oil or sulfonated alcohol than after the use of toilet soaps. And it was demonstrated that soap substitutes were occasional irritants.[8a]

A PROPER TECHNIC FOR THE USE OF SOAP

The patient may be given a list of four or five common white toilet soaps so that he may try them all and use the one he prefers. Thus, if his skin is irritated by a perfume, filler or other ingredient of one soap, he will be able to select another which is nonirritating. A cake of shaving soap may be substituted if no toilet soap proves satisfactory. The harder the water the more soap will be required for washing and the more precipitate will have to be rinsed off the skin. But this hardness cannot be changed, unless a water-softening device is installed. I have always felt that a generous supply of hard water is preferable to an insufficient amount of soft water. Soap dissolves better in warm water, but the water should not be so warm or the bath so prolonged as to cause maceration of the epidermis. The duration of the bath should be just sufficient for thorough cleansing. As a rule, the patient should be instructed to bathe not oftener than once a day and to wash the face briefly two or three times a day and the hands more frequently if necessary. Hansen [5a] observed that it took three and one-half hours for the p_H of the skin of the forearm to return to normal after two minutes of washing but only a half-hour if the patient was perspiring profusely. Rinsing must be thorough in order to remove all traces of soap and precipitates from the skin, and with hard waters extra rinsing is required. A shower bath or bath spray is ideal for this purpose. Even after thorough rinsing the skin is left too alkaline, and an interval will be required for its reaction to return to normal.[17] This interval varies with the person. Thorough drying is necessary to prevent maceration, and the towel should not be so rough as to injure the skin. After drying, if the skin shows evidence of lack of oil, a suitable bland oil should be applied, rubbed in fairly well and then wiped off so that the skin is not greasy. A little plain talcum may then be applied if desired. For a number of years I have outlined this technic, step by step, in the form of written directions, for many patients, and I have heard no complaints and have not had to advise soap substitutes.

SUMMARY AND CONCLUSIONS

Excellent low-priced toilet soaps are available. They are unexcelled as cleansing agents, and their hygienic value makes them indispensable for daily use.

17. Lustig, B., and Schmerda, F.: Ueber die Löslichkeit der Natriumseifen. Ein Beitrag zur Pharmakologie der Seifenwirkung, Dermat. Wchnschr. **104**:607, 1937; abstracted, Zentralbl. f. Haut- u. Geschlechtskr. **58**:636, 1938. Sharlit and Scheer.[6]

As I have shown, when these soaps are used with hard waters rather large precipitates are formed, chiefly calcium and/or magnesium soaps. I have shown by patch tests that these precipitates do not irritate the normal skin.

Sulfonated oil leaves an oily residue in hard waters, and sulfonated alcohol also leaves a slight residue. Patch tests with these residues gave negative results.

A proper technic for washing is outlined. A patient may select and use the toilet soap he prefers, with the aid of the physician, who gives detailed written instructions regarding the temperature and duration of the bath, the frequency of washing and the need for thorough rinsing and drying and for the application of a bland oil afterward to prevent undue dryness. This technic has proved satisfactory, and no soap substitutes have been required.

ABSTRACT OF DISCUSSION

Dr. James Herbert Mitchell, Chicago: I was somewhat surprised to hear Dr. Parkhurst say that all toilet soaps are perfectly safe and to be recommended. I recall numerous instances of the use of toilet soaps which have produced irritation and which on patch tests have demonstrated that they were definitely active. One of the most widely advertised of all soaps, particularly the shaving cream, has, in my experience, caused definite erythematous dermatitis in a large number of cases. Many of these soaps probably are irritating because of their color or their perfume. For that reason, I think it is well to avoid anything in the way of so-called toilet soap. A simple soap like one of the best known, white, unperfumed, uncolored soaps is, in my experience, best of all.

Making the patch test with the soap itself is not always satisfactory. I tried patch testing a number of times after hydrolyzing the soap, in other words, adding water and making a suds. Thus a positive result to a patch test is obtained with some of the soaps that would not produce it otherwise.

I should like to ask Dr. Parkhurst if he has not had any irritation with the widely advertised brands of toilet soap.

Dr. Earl D. Osborne, Buffalo: I gained the impression that Dr. Parkhurst stated that toilet soaps were of little importance in the production of eczema. I cannot agree with that conclusion, and I think that experiments reported in the literature and work that I have done will substantiate that.

One must remember that even the highest grade soaps in solution have a p_H of 10 to 12. Therefore, one can never escape the primary irritation from the effects of the alkali content of soap in solution. The effect of this primary irritation from the alkali content must always be differentiated clinically from true hypersensitivity of the skin to certain specific soap ingredients. I believe that the common hospital itch, occurring particularly on areas of contact of the skin with bed linen, is due to the irritative action of the alkali.

This brings up the interesting question of the effect of laundry chemicals retained in all linen, after even the most efficient laundering processes. With the use of soap, insoluble precipitates of calcium and magnesium, united with the fatty acids, are always formed and give rise to the well known rim on the tub. This precipitate is always present in the fibers of all fabrics after laundering with soap. The laundering industry has studied this from a microscopic stand-

point. Fabrics have been washed under all conditions, with the finest soap and innumerable rinsings. Microscopic examination showed that with repeated washing the insoluble precipitate always piles up on the fibers of all fabrics. Ordinary chemical tests will not reveal the presence of these precipitates. The p_H of the rinsings is normal. The solution is clear. However, under the influence of contact with the human body, including sweat, these insoluble precipitates are gradually redissolved and act as constant irritants. This is an explanation according to common sense and logic of primary irritation seen clinically in many cases of ordinary hospital itch and in many cases of pruritus ani and pruritus vulvae. In bathing, soaps are rubbed into the folds and crypts of these parts. Thorough removal by rinsing is impossible. The calcium and magnesium precipitates and the fatty acids formed gradually set up an irritation, producing pruritus. What one sees, of course, is the result of scratching and rubbing. Careful attention to these details is of extreme value in curing pruritus ani and pruritus vulvae in many cases.

I firmly believe that there is definite, specific, allergic response to certain ingredients in soaps. I have proved the etiologic factor of soap ingredients, other than alkali, in a large number of cases of eczema. Patch tests and clinical observations have proved this. Soaps in general are known to contain at least thirty different ingredients which, individually, are known to be active sensitizing agents. It should be self evident that these substances can produce hypersensitivity of the skin after prolonged contact.

Blank has shown admirably the important place of alkalinity in the production of eczema from soap. The higher the alkalinity, the more rapidly eczematization occurs. (Blank, I. H.: Action of Soap on Skin, ARCH. DERMAT. & SYPH. **39**:811-824 [May] 1939).

One more practical point which may be of some interest is the employment of sulfonated alcohol in small amounts in bath water sufficient to prevent the formation of the insoluble calcium and magnesium precipitates. A small amount of this substance sprinkled in a tub of water enhances the value of the bath considerably.

DR. H. J. TEMPLETON, Oakland, Calif.: One way of cleansing the hands, especially the badly soiled hands of workingmen with eczema, that I have used is an old farm trick. Simply have the patient put some finely ground yellow corn meal in his hands, make a paste of it and wash with that. It is well tolerated by many patients with eczema and represents a good cleanser.

DR. W. W. DUEMLING, Fort Wayne, Ind.: I should like to ask Dr. Parkhurst if his observations on patch tests on men differed from those on women.

Emery and Edwards (Emery, B. E., and Edwards, L. D.: Tri-Isopropanolamine Salts Used in Making Cold Cream, *Drug Trade News* **12**:27 [Aug. 28] 1937) studied the potassium and sodium soaps of nine pure fatty acids. They reported that the potassium soaps are more irritating than the corresponding sodium soaps. They also stated:

"The pure sodium alkyl sulfates [a soap substitute] are less irritant to the human skin than the corresponding pure sodium or potassium salts of the saturated fatty acids containing 8 to 18 carbons. Sodium lauryl sulfate was found to be the most frequent cause of skin irritation of the series studied, closely followed by sodium myristyl sulfate. The irritant action of these soap substitutes is considerably increased in the presence of sodium chloride and sodium sulfate and especially in the presence of sodium carbonate."

DR. HOWARD J. PARKHURST, Toledo, Ohio: As the title of the paper indicates, I tested persons not for susceptibility to soap but for susceptibility to the precipitate

which formed when soap was used with hard water. I did not mean to convey the impression that all toilet soaps are safe to use. I distinctly stated that hard water castile soap should not be recommended because it renders the skin readily alkaline. Also, on account of the large amount of oily precipitate, which is hard to rinse off, the popular olive oil toilet soap and the superfatted soaps are not recommended.

However, it is my suggestion that one is safe in recommending to patients a few of the common white toilet soaps which are obtained cheaply at all groceries, leaving out those which are likely to irritate. Then, if the proper washing technic is used, as I outlined, I do not feel that there will be much difficulty.

Toilet soaps may produce eczema, I agree with Dr. Osborne, if they are used indiscriminately and with improper washing technic. If they are used with the proper technic, I do not think they are likely to cause such a condition.

I also have observed many cases in which the skin was irritated by contact with linen which had been laundered with the strong laundry soaps that are so popular and in which this irritation disappeared rather promptly after the substitution of a milder laundry soap and more thorough rinsing with extra waters. I believe that the matter of technic is important.

In answer to Dr. Duemling, these patch tests were made almost entirely on women, and almost entirely on young women.

A COMPARATIVE STUDY OF SEROLOGIC TESTS FOR SYPHILIS

LESTER HOLLANDER, M.D.

CHARLES L. SCHMITT, M.D.
AND
CLARA R. SCHLESINGER, B.A.
PITTSBURGH

Since the fall of 1934 we have been particularly concerned with the evaluation of various serologic tests for syphilis. In three previous reports [1] we presented some of our findings. Each report dealt with the results obtained in 3,000 consecutive patients, and in each report the Wassermann tests (with the acetone-insoluble lipoid antigen and with the cholesterolized antigen), the Kahn test (precipitation) and the Hinton test (flocculation) were compared as to sensitivity and reliability.

Interpretation of these studies indicated that in a careful serologic survey no single serologic test can be accepted as critical, that such a serologic survey should include at least four of the available procedures and, further, that obtaining a careful clinical history and a meticulous physical examination are just as important today as they were before laboratory help was as readily available.

MATERIAL

Our present report deals with the evaluation of the same four serologic tests as computed from the study of 15,000 consecutive patients who attended our clinic on account of either a cutaneous disease or cancer.

The distribution of sexes was almost equal, as 7,465 were males and 7,535 were females. Thirteen thousand and three, or 86.69 per cent were white and 1,997, or 13.31 per cent, were colored. Of the white persons 6,527, or 50.19 per cent, were males and 6,476, or 49.81 per cent, were females; of the colored persons 938, or 46.97 per cent, were males and 1,059, or 53.03 per cent, were females.

From the Pittsburgh Skin and Cancer Foundation.

1. Hollander, L.; Schlesinger, C. R., and Schmitt, C. L.: The Hinton Test for Syphilis: A Study of Its Clinical Value in Three Thousand Patients, Urol. & Cutan. Rev. **39**:617 (Sept.) 1935; The Hinton Test for Syphilis: The Second Study of Its Clinical Value in Three Thousand Patients, J. Lab. & Clin. Med. **22**:97 (Oct.) 1936; The Hinton Test for Syphilis: The Third Study of Its Clinical Value in Three Thousand Patients, ibid. **23**:536 (Feb.) 1938.

Of the white persons 1,599, or 12.29 per cent, showed a positive reaction to one or more tests; of these 941 were males and 658 were females. Of the colored persons, 838, or 41.95 per cent, showed a positive reaction to one or more tests; of these 368 were males and 470 were females.

A doubtful reaction occurred in 44, or 0.33 per cent, of the white patients; of these 19 were males and 25 females. A doubtful reaction occurred in 16, or 0.81 per cent, of the colored persons; of these 6 were males and 10 females.

COMPARISON OF THE TESTS

A positive Wassermann (with the acetone-insoluble lipoid antigen) reaction occurred in 1,348 patients. Twenty-five gave an anticomplementary reaction.

A positive Wassermann (with the cholesterolized antigen) reaction occurred in 1,615. Twenty-five gave an anticomplementary reaction.

A positive Kahn reaction occurred in 1,846.

A positive Hinton reaction occurred in 2,363.

The analysis of the 2,437 positive reactions shows the following facts and requires no further comment.

The Kahn and the Hinton reactions were negative and the two Wassermann reactions positive in 12. All the tests gave negative results except one Wassermann test (acetone-insoluble lipoid) in 2 white patients. All gave positive results except one Wassermann test (cholesterolized) in 6 cases. All gave positive results except the other Wassermann test (acetone-insoluble lipoid) in 215.

The Wassermann (cholesterolized) and the Kahn reactions were positive and the other two negative in 5 white patients. The Wassermann (cholesterolized) and the Hinton reactions were positive and the other two negative in 25 patients. The Wassermann (cholesterolized) reaction alone was positive in 30. The Kahn and the Hinton reactions were positive and the other two negative in 283 patients.

The Kahn and the Hinton reactions were positive and the other two anticomplementary in 19 patients. The Kahn reaction alone was positive in 19. The Hinton reaction alone was positive in 493 patients.

Thus, we found in 544 persons a positive reaction to a single serologic test, which by itself was of little value and needed some form of confirmation. Considering the medical history, the result of physical examination and previous antisyphilitic treatment each as a separate factor for verification of these positive reactions to single tests, we obtained the following information:

The Wassermann (acetone-insoluble lipoid) reaction alone was positive in 2 white patients. Physical findings confirmed the result in 1 patient, leaving one unconfirmed reaction, which was considered false.

The Wassermann (cholesterolized) reaction alone was positive in 30 patients. A history of syphilis and of previous antisyphilitic treatment confirmed this result in 10 white patients. Thus, with this test there occurred 20 positive reactions which were considered false.

The Kahn reaction alone was positive in 19 patients. In 4 the result was confirmed by a history of syphilis and of previous antisyphilitic treatment, and in 2 it was confirmed by physical findings. Thirteen reactions remained unconfirmed and were considered false.

The Hinton test alone gave positive results in 493 patients. In 264 of these the result was confirmed by physical findings and by a history of previous antisyphilitic treatment. In 45 additional patients the result was confirmed by a history of syphilis by physical findings. In 31 additional ones it was confirmed by a history of syphilis. Six additional positive reactions were confirmed by physical findings and by a history of previous antisyphilitic treatment. Fourteen more were confirmed by physical findings. Nineteen were confirmed by a history of previous antisyphilitic treatment. Nine additional were confirmed by a history of syphilis and of previous antisyphilitic treatment. Six additional were considered confirmed because of a history which was thought questionable enough to be taken as indicative of syphilis. Twenty-six additional reactions were confirmed by tests of the spinal fluid. Five others were confirmed by other serologic tests at a later period. Thus, there were 68 unconfirmed reactions, which were considered false.

ANALYSIS OF THE NEGATIVE REACTIONS

The patients with negative reactions to the Wassermann test (acetone-insoluble lipoid antigen) who gave positive reactions to other serologic tests numbered 1,070. One hundred and nineteen gave positive Kahn and Hinton reactions, histories of syphilis and had received previous antisyphilitic treatment. Eighty-six had positive Kahn and Hinton reactions, histories of syphilis and physical evidence. Seven had positive reactions to the Kahn and the Hinton tests and had physical evidence. Twenty-nine had positive reactions to the Kahn and the Hinton tests, histories and physical evidence of syphilis and previous antisyphilitic treatment. Twenty-six had positive reactions to the Kahn and the Hinton tests and had histories of syphilis. Sixteen gave positive reactions to the Kahn and Hinton tests and had received previous antisyphilitic treatment. Twenty-one patients had positive reactions to a Wassermann (cholesterolized antigen) and the Hinton test, histories of syphilis and previous antisyphilitic treatment. Four gave positive Wassermann (cholesterolized) and Hinton reactions and received previous antisyphilitic treatment. Eighty had positive reactions to the other three serologic tests.

Of the total 1,070 negative reactions to the Wassermann (acetone-insoluble lipoid antigen) test, 101 were considered unconfirmed because they were positive to only one of the critical factors. We therefore estimated that the Wassermann (acetone-insoluble lipoid) test failed in 969 patients, of whom 653 were white and 316 were colored. These figures would indicate that the failure of the Wassermann (acetone-insoluble lipoid) test among colored persons was much more frequent thant it was among white ones.

In the analysis of the patients with negative Wassermann (cholesterolized antigen) reactions and positive reactions to other serologic tests, there was a total of 803, of whom 541 were white and 262 were colored. Of the 803, the reactions in 82 were unconfirmed, 721 patients being left in whose cases the Wassermann (cholesterolized antigen) test failed. Of these 481 were white and 240 were colored, which shows that again there was a much greater percentage of failure among the colored than among the white patients.

The analysis of the patients with negative reactions to the Kahn test but positive reactions to the other serologic tests revealed 591, of whom 413 were white and 178 were colored. Of the 591, the reactions of 96 remained unconfirmed, leaving 495 patients for whom the Kahn test failed, of whom 343 were white and 152 were colored.

The patients with negative reactions to the Hinton test and positive reactions to other serologic tests numbered 74; of these 61 were white and 13 were colored. Of the 74 the results in 42 were unconfirmed, showing that the Hinton test failed in 32 patients, of whom 29 were white and 3 colored.

COMMENT

These figures seem to speak for themselves. Of 15,000 consecutive patients, roughly speaking, 13,000 were white with the sexes evenly divided and 2,000 were colored with females predominating by about 6 per cent. Of the white persons 1,599, or 12.29 per cent, gave positive serologic reactions, as compared with 41.95 per cent of the colored, which seems to indicate that in any study of this type the results of the tests in white patients must necessarily be separated from those in colored patients in order to obtain an accurate estimate of the prevalence of the disease. The disproportion between the white and the colored patients was too great to be thrown into the same percentage column.

Among the white patients, 17 per cent more of the males than of the females had positive serologic reactions, while among the colored patients the females gave positive reactions in 12 per cent more cases than the males. Thus it would seem that for the correct understanding of syphilis distribution it should be essential that the figures be divided into the

four brackets—that is, the division of the color and the division of the sex—in order that anything like a true picture be obtained. In our study the colored females showed the highest percentage and the white females the lowest percentage of syphilis.

We believe that a valuable picture was gained from the comparison of the methods used, showing that the most sensitive of the four tests used was the Hinton test, followed by the Kahn, then by the cholesterolized antigen Wassermann and lastly by the acetone-insoluble lipoid antigen Wassermann. We believe that this is a well known observation.

It is the breakdown of the figures, however, which we believe shows the real status of affairs. Of the 15,000 patients there were 442 who

Complete Analysis of the Positive Reactions to Serologic Tests

Results of Serologic				Patients		
Wassermann (Lipoid Antigen)	Wassermann (Cholesterolized Antigen)	Kahn	Hinton	White	Colored	Total
+	+	+	+	819	474	1,293
+	+	—	+	20	9	29
+	+	+	—	5	1	6
+	+	—	—	11	1	12
+	—	—	—	2	0	2
+	—	+	+	3	3	6
—	+	+	+	145	70	215
—	+	+	—	5	0	5
—	+	—	+	16	9	25
—	+	—	—	24	6	30
—	—	+	+	182	101	283
Anticomplementary	Anticomplementary	+	+	13	6	19
—	—	+	—	14	5	19
—	—	—	+	340	153	493
				1,599	838	2,437

gave positive results to but one of the four serologic tests and were later found to be syphilitic. The utilization of these four tests uncovered 2.94 per cent of the patients who otherwise would have gone unrecognized, as every test produced 1 or more patients in whom all the other three tests failed.

False reactions also showed an interesting picture. Of these, only 1 occurred among the patients giving positive reactions to the Wassermann test with acetone-insoluble lipoid antigen. The number of false positive reactions was higher with the Wassermann test with cholesterolized antigen than with the Kahn test, even though the latter gave positive reactions in a much larger number of patients than did the Wassermann test with cholesterolized antigen, thus leaving the field definitely in favor of the Wassermann test with acetone-insoluble lipoid antigen and the Kahn test. The failure of the Hinton test was so infrequent as

to be astonishing. While the other tests failed in from 595 to 696 patients, the Hinton failed in 32 only; on the other hand, it also showed the greatest number of false positive reactions.

CONCLUSIONS

As in our previous communications, so again in this one we think that we are justified in drawing the following conclusions:

1. For a complete serologic survey the larger the number of tests which are performed on the individual serum the greater the accuracy of the result.

2. Although the Hinton test is the most sensitive of those which we have investigated, it failed in a sufficient number of instances to make its fallibility apparent; moreover, it showed the largest number of false positive reactions.

3. Any statistical study on the prevalence of syphilis in population groups must be divided as to white and colored and male and female patients to obtain a fairly accurate picture.

LAUGHLEN TEST FOR SYPHILIS

JOHN F. STECKER, M.D.

P. H. GREEY, M.D.

AND

E. I. PAUL

TORONTO, CANADA

In a previous communication [1] the routine use of the Laughlen test [2] for syphilis in blood donors was described. The test was observed to be of value as an exclusion test, provided that the serum was inactivated prior to use, but a sufficient number of false positive results were obtained to indicate that the test might not be suitable as a diagnostic procedure. The present extended investigation of the Laughlen test deals with the thermal conditions necessary for the satisfactory inactivation of serum and a study of the accuracy of the test in the presence of various clinical conditions.

The preliminary work referred to was concerned with the value of the Laughlen test with (*a*) fresh unheated serum, (*b*) stored serum and (*c*) inactivated serum. In 10 per cent of the fresh unheated serums from syphilitic persons the reaction was negative, but the same serums stored for several days or inactivated at 56 C. for thirty minutes all gave positive reactions. The thirty minutes required for inactivation of serum is, however, a definite drawback to the use of the Laughlen test in connection with a transfusion service. Laughlen [2] stated that ten minutes' heating at 56 C. gives satisfactory results, and Rein and Hazay [3] asserted that heating at 63 C. for five minutes or at 69.5 C. for only one minute is adequate. However, comparative figures on the accuracy of the Laughlen test at these temperatures and times were not given, and since inactivation of the serum is important in the test, this phase of the subject was studied more thoroughly.

From the Department of Bacteriology of the Toronto General Hospital.

1. Greey, P. H.; Bracken, M. M., and Paul, E. I.: The Laughlen Test and Blood Donors, Canad. M. A. J. **42**:126, 1940.

2. Laughlen, G. F.: A Rapid Test for Syphilis, Canad. M. A. J. **33**:179, 1935.

3. Rein, C. R., and Hazay, C. E.: The Laughlen Test for Syphilis, J. Invest. Dermat. **1**:283, 1938.

TECHNIC

The following technic was used for the performance of the tests described in this paper.

Usually twenty tests were performed at one time by placing approximately a drop of inactivated serum on a section of a large glass plate ruled in 1 inch (2.5 cm.) squares. To the serum was added a similarly sized drop of activated Laughlen reagent (Lederle). The serum and the reagent were thoroughly mixed with an applicator stick, and the slide was then constantly oscillated from side to side at the rate of fifteen to twenty times each minute for ten minutes. The test was read by holding the slide above and a little to one side of a strong, shaded light, with a dull black surface forming a background. Serums giving strongly positive reactions were recognized by the appearance of large coarse red granules in an almost colorless field, while those giving positive or weakly positive reactions showed correspondingly smaller granules. Serums giving negative results, as a rule, retained a homogeneous translucent pink color during the whole period of observation. A positive and a negative control were also made for purposes of comparison, as well as to check the stability of the stock reagent.

While over 95 per cent of the serums studied gave either frankly positive or negative reactions, as is true of most precipitation tests, difficulty was encountered in interpreting the reaction of the remainder. Occasionally a normal serum would show a slight colorless granulation without definite clumping; in such cases the persistence of a pink field indicates that the reaction is negative. Reactions of this type require experience to interpret; the tendency at first is to read them falsely as positive. The test should not be read with the aid of a microscope, since errors in interpretation will result.

Laughlen stated that the time required for the reaction to become visible is an index of the degree of positivity of the specimen. To some extent this may be true. The specimens giving strongly positive reactions will, as a rule, react in the first few minutes, but it is not uncommon for serums giving weakly positive reactions to do likewise. We have found that with constant oscillation of the slide the degree of positivity may best be judged by the size of the granules: the coarser the granules, the more positive the reaction of the serum. After some experience one may, by careful comparison with the results of the Kahn or similar tests, acquire considerable accuracy in classifying the degree of positivity by means of the size of the agglutinates.

INACTIVATION

Specimens were obtained from 143 syphilitic persons. Each serum was divided into four parts, one of which was not heated. The second portion was heated at 56 C. for ten minutes, the third at 56 C. for thirty minutes and the fourth at 62 C. for three minutes. Each was tested with the Laughlen test, and the results are shown in table 1. Of the 143 serums, 15 (11.7 per cent) gave negative reactions when unheated, but all gave positive reactions after inactivation at the temperatures and times stated. It was also noted that a number of specimens which gave weakly positive reactions when unheated showed stronger reactions after heating.

These results again emphasize the need of inactivating the serum before using the Laughlen test and indicate that heating at 62 C. for three minutes is satisfactory for tests on blood donors.

SUMMARY OF THE LITERATURE

In his first paper Laughlen published results on two series of cases. In a series of 400 specimens examined by himself, the Laughlen test agreed with the Wassermann test in 98 per cent of cases and with the Kahn test in 99 per cent. In the second series of 118 specimens, obtained at the Toronto East General Hospital, the Laughlen test agreed with the Wassermann test in 93.5 per cent of cases and with the Kahn test in 97 per cent. Similar favorable results have since been obtained by other investigators.[4] Lever and Massie,[5] reporting recently on 3,000 specimens from the Massachusetts General Hospital, observed an average

TABLE 1.—*Comparison of Laughlen Reactions of Heated and Unheated Serums from Syphilitic Persons*

Laughlen Reaction	Unheated	Heated		
		56 C. for 10 Minutes	56 C. for 30 Minutes	62 C. for 3 Minutes
Positive	128	143	143	143
Negative	15	0	0	0
Percentage of negative reactions	11.7	0	0	0

specificity of 99.3 per cent and a sensitivity of 76.2 per cent for the Laughlen test. On the other hand, several investigators,[6] having obtained

4. Robinson, F. H., and Stroud, G. M.: Laughlen's Test for the Serodiagnosis of Syphilis, J. A. M. A. **108**:1170 (April 3) 1937. Price, A. S.: The Laughlen Test for Syphilis, New York State J. Med. **39**:880, 1939. Craig, H. W., and Callaway, J. L.: A Study of the Sensitivity and Specificity of the Laughlen Test, Am. J. Syph., Gonor. & Ven. Dis. **23**:76, 1939. Beck, R. C.: The Laughlen Test for Syphilis, Am. J. Clin. Path. **9**:151, 1939. Dienst, R. B., and Sanderson, E. S.: The Laughlen Test as Compared to the Kahn and Modified Kolmer Serodiagnostic Tests for Syphilis, Am. J. Syph., Gonor. & Ven. Dis. **22**:699, 1938. Walters, A. T. J.: The Laughlen Rapid Test for Syphilis, Brit. J. Ven. Dis. **15**: 228. 1939. Gunn, W. D.: Laughlen Modified Test, J. Roy. Nav. M. Serv. **25**: 157, 1939.

5. Lever, W. F., and Massie, W. K.: The Laughlen Test, Arch. Dermat. & Syph. **40**:45 (July) 1939.

6. Usher, G. S.: An Appraisal of the Laughlen Test for Syphilis, Am. J. Syph., Gonor. & Ven. Dis. **22**:452, 1938. Muether, R. O., and Greutter, J. E.: Comparative Study of Laughlen Test, J. Lab. & Clin. Med. **24**:212, 1938. Flood, J. M., and Mayer, V.: Inadequacy of the Laughlen and the Ide Test, Arch. Dermat. & Syph. **39**:510 (March) 1939. Rein and Hazay.[3]

a high percentage of false positive and/or false negative reactions, concluded that the Laughlen test should not be used as a serodiagnostic procedure but would be most useful as an exclusion test for syphilis.

ACCURACY OF THE LAUGHLEN TEST IN THE PRESENCE OF VARIOUS CLINICAL CONDITIONS

In order to gain further information as to its accuracy, the Laughlen test was applied to the serums of over 1,000 persons. These included 300 healthy, presumably nonsyphilitic persons (medical students, orderlies, nurse aids and blood donors). In the clinical group were 526 patients from the medical and surgical wards (syphilis being reasonably excluded by the history and physical examination), 71 untreated patients with syphilis and 207 patients with early and late stages of syphilis who had had varying amounts and kinds of treatment. The other

TABLE 2.—*Analysis of Reactions of Kahn, Wassermann and Laughlen Tests on Syphilitic Persons*

Clinical Condition	No. of Subjects	Test	Reactions				
			Strongly Positive	Weakly Positive	Negative	Total No. Positive	Per Cent Positive
Early or late syphilis, untreated	71	Wassermann	67	4	0	71	100
		Kahn	69	2	0	71	100
		Laughlen	64	5	2	69	97
Syphilis, treated	230	Wassermann	59	82	89	141	61.3
		Kahn	65	89	76	154	66.9
		Laughlen	72	131	27	203	88.2

groups studied consisted of presumably nonsyphilitic patients: 50 with tuberculosis, 50 with malignant neoplastic diseases, 50 with acute febrile diseases (temperature above 100 F.), 50 normal pregnant women, 25 patients with jaundice due to varying causes and, lastly, 25 women during menstruation. Kahn tests were performed on every specimen, while the Wassermann test was performed only on serums from persons with known syphilis in this series.

RESULTS

The results obtained in syphilitic persons are recorded in table 2. In all 71 untreated patients with early and late syphilis, the Wassermann and Kahn tests gave positive reactions. However, the Laughlen reaction was negative in 2 untreated patients with early syphilis, and tests on these 2 one week later still gave negative results. In 230 syphilitic persons with varying amounts and kinds of treatment positive reactions to the Wassermann test were obtained in 141, to the Kahn test in 154

and to the Laughlen test in 203. From these results it would seem that the Laughlen reaction remains positive in a treated syphilitic person longer than either the Kahn or the Wassermann reaction. However, in 4 treated patients with strongly positive Kahn and Wassermann reactions the Laughlen reaction was negative.

Table 3 presents the results obtained in 1,076 nonsyphilitic persons. Of the 300 healthy, nonsyphilitic ones, who gave negative Kahn reactions, only 1 had a false positive Laughlen reaction, giving a specificity of 99.7 per cent for normal persons. On the other hand, of the 526 nonsyphilitic patients suffering from varied medical and surgical conditions, 9 (1.71 per cent) gave false positive Laughlen reactions. Furthermore, false positive reactions were encountered in patients with tuberculosis, malignant neoplastic disease and acute febrile conditions from

TABLE 3.—*Results of Laughlen Test on Nonsyphilitic Persons of Various Clinical Groups in Which the Kahn Test Gave Negative Results*

Clinical Condition	No. of Specimens	False Positive Reactions		Per Cent Specificity
		Number	Per Cent	
Normal health	300	1	0.3	99.70
Medical and surgical conditions	526	9	1.71	98.29
Pregnancy	50	0	0	100
Tuberculosis	50	2	4	96
Malignant neoplastic diseases	50	1	2	98
Acute febrile diseases	50	2	4	96
Jaundice	25	0	0	100
Menstruation	25	0	0	100
Total	1,076	15	Average 1.5	98.5

various causes. Jaundice, pregnancy and menstruation did not cause the appearance of false positive reactions in the groups tested. A careful recheck of the history with further physical examination for evidence of syphilis was made on all patients available who gave a positive Laughlen reaction and a negative Kahn reaction. While the relative number of serums tested in each group is small, it serves to establish the fact that false positive reactions to the Laughlen test do occur and apparently are more frequent in some groups than in others.

COMMENT

After a study of five official evaluations of tests for syphilis, Nagel and Willet [7] concluded that a serodiagnostic test should possess a minimum specificity of 99 per cent. The Committee on Evaluation of Sero-

7. Nagel, N., and Willet, J. C.: What Did Five Official Evaluation Studies of Tests for Syphilis Reveal? Am. J. Syph., Gonor. & Ven. Dis. **22**:231, 1938.

diagnostic Tests for Syphilis,[8] cited by Parran and his associates, recommended: "An efficient serodiagnostic test for syphilis should possess specificity of 100 per cent. Any test which yields even one per cent of false positive reactions should be so modified as to increase its specificity even with some slight sacrifice of sensitivity." In this study the sensitivity of the Laughlen test was satisfactory, but the test did not reach this high standard of specificity. For this reason, we believe that the usefulness of the test is limited. It should not be used as a serodiagnostic procedure but can serve well as a quick exclusion test and is particularly suitable for use in connection with a blood transfusion service. The Laughlen test is indeed a quick, easy and economical test but requires experience in the interpretation of the end point.

CONCLUSIONS

1. Serums must be inactivated prior to the application of the Laughlen test. Since in 143 serums identical results were obtained by heating at 56 C. for thirty minutes, at 56 C. for ten minutes and at 62 C. for three minutes, any of these temperatures and times should prove satisfactory.

2. The Laughlen test gave a specificity of 98.5 per cent in a group of 1,076 nonsyphilitic persons.

3. The incidence of positive Laughlen reactions was found to be higher than that of Kahn or Wassermann reactions in treated syphilic patients, suggesting that the reaction to this test remains positive longer than that of either of the others.

4. The Laughlen test provides a quick exclusion test for syphilis.

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8. Parran, T.; Hazen, H. H.; Sanford, A. H.; Senear, F. E.; Simpson, W. M., and Vonderlehr, R. A.: The Efficiency of State and Local Laboratories in the Performance of Serodiagnostic Tests for Syphilis, Ven. Dis. Inform. **18**:4, 1937.

THE ADEQUATE DIAGNOSIS OF INFANTILE CONGENITAL SYPHILIS

NORMAN R. INGRAHAM JR., M.D.

BERTRAM SHAFFER, M.D.

BARBARA E. SPENCE, R.N.

AND

JAMES H. GORDON, M.D.

PHILADELPHIA

Recently the opportunity has been afforded to review in considerable detail the results obtained in a study [1] completed about five years ago in which was described a clinical method of approach to the often difficult problem of diagnosing congenital syphilis in the first few weeks of postnatal life. The restudy of this material seemed especially pertinent and essential in the light of the recent applications of advancing knowledge of the quantitative estimation of syphilis reagin in the infant's blood stream (Faber and Black,[2] Christie [3] and Davies [4]) and of the effect of infantile diseases or malnutritional states other than syphilis (Caffey,[5]

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From the Prenatal Syphilis Clinic, Philadelphia General Hospital; the Department of Dermatology and Syphilology, University of Pennsylvania School of Medicine, and the University of Pennsylvania Institute for the Control of Syphilis, with the cooperation of the Pennsylvania State Department of Health.

1. Ingraham, N. R., Jr.: The Diagnosis of Infantile Congenital Syphilis During the Period of Doubt, Am. J. Syph. & Neurol. **19**:547 (Oct.) 1935.

2. (*a*) Faber, H. K., and Black, W. C.: Quantitative Wassermann Tests in the Diagnosis of Congenital Syphilis: Clinical Importance of Fildes' Law, Am. J. Dis. Child. **51**:1257 (June) 1936. (*b*) Black, W. C.: Diagnosis of Congenital Syphilis: Pathognomonic Criteria, J. Pediat. **14**:761 (June) 1939.

3. Christie, A. U.: Diagnosis of Syphilis in New-Born Infants: Use of Quantitative Wassermann Tests, Am. J. Dis. Child. **55**:979 (May) 1938.

4. Davies, J. A. V.: (*a*) A "Rapid" Micro-Hinton and Capillary Hinton Test for Syphilis, with a Discussion of the Detection of Syphilis by Serologic Methods, J. Pediat. **10**:802 (June) 1937; (*b*) The Evaluation of Serologic Tests for Congenital Syphilis with Special Reference to the Neonatal Period, ibid. **13**: 341 (Sept.) 1938.

5. Caffey, J.: Syphilis of the Skeleton in Early Infancy: The Nonspecificity of Many of the Roentgenographic Changes, Am. J. Roentgenol. **42**:637 (Nov.) 1939.

Aries [6] and Evans [7]) and of antisyphilitic therapy administered to the mother prepartally (Caffey,[8] Christie [9] and Whitridge [10]) on the interpretation of the roentgenogram of the infant's long bones during the neonatal period. At the time of the original study the possibility of the transfer of complement-fixing substance from the maternal to the fetal circulation before birth was recognized, but the facilities for its quantitative estimation were not immediately available, with the result that arbitrary rules had to be established in regard to the rate of disappearance of this substance from the blood stream of the nonsyphilitic infant. The effect of prepartal treatment of the mother on the roentgenographic findings in the infant was hardly recognized and certainly not clearly understood. Fortunately, from the standpoint of the original study, the maternal antisyphilitic treatment was such that of the 239 pregnant women in the series only 9 received bismuth therapy—apparently the chief offender from the diagnostic standpoint—close enough to term to have any effect on roentgenographic interpretation, and it is felt that inaccurate diagnosis as a result of such an error, with what was possibly unjustifiable institution of treatment for syphilis in an infant who was probably not syphilitic, resulted only twice. This type of diagnostic error, on the other hand, is minimized to some extent by the fact that the infants of 2 of the remaining 7 patients treated largely with a bismuth compound during the pregnancy because of intolerance to arsenicals showed clinical evidence of syphilis and were discovered to have positive serologic reactions of the blood for this disease at the age of 7 and 8 months respectively.

PRESENTATION OF MATERIAL

At the time of the original presentation, in June 1935, it was considered possible either to establish or to eliminate the diagnosis of syphilis in the infant offspring of 219 of the 239 pregnant women studied. Persistent effort subsequent to that date made it possible to propose an initial diagnosis in 11 additional cases, bringing the total to 230. In 9 cases the follow-up observations were insufficient to make possible even an initial diagnosis of infantile syphilis. In the original presenta-

6. Aries, P. L.: Roentgen Study of Osseous Development in the Newborn, with Special Reference to Congenital Syphilis, Am. J. Dis. Child. **59**:908 (April) 1940.

7. Evans, W. A., Jr.: Syphilis of the Bones in Infancy, J. A. M. A. **115**: 197 (July 20) 1940.

8. Caffey, J.: Changes in the Growing Skeleton After the Administration of Bismuth, Am. J. Dis. Child. **53**:56 (Jan., pt. 1) 1937.

9. Christie, A. U.: The Value of Roentgenographic Examination in the Diagnosis of Syphilitic Newborn Infants, J. Pediat. **15**:230 (Aug.) 1939.

10. Whitridge, J.: Changes in the Long Bones of Newborn Infants Following the Administration of Bismuth During Pregnancy, Am. J. Syph., Gonor. & Ven. Dis. **24**:223 (March) 1940.

tion, likewise, it was arbitrarily assumed that all stillbirths and deaths of infants of syphilitic mothers occurring within the first twenty-four hours, 27 in number, were the result of syphilis. Subsequent study has indicated that in all probability 6 of these deaths could be explained on the basis of causes other than syphilis and that this disease was probably not of primary importance. The revised figures, therefore, reveal that of the 230 infants adequately studied 111 (48.3 per cent) were syphilitic and 119 (51.7 per cent) nonsyphilitic. In connection with the high percentage of syphilitic children in this series and the high mortality in the diseased group, it is to be recalled that from 1933 to 1935 in the clinic from which this report emanates no active follow-up service was available, and hence treatment in some instances was irregular and inadequate for both mother and child. Fortunately, the employment of the full time public health nurse, which made this reevaluation study possible, has largely rectified this situation. We have been able to learn the ultimate outcome in the cases of 82 (73.9 per cent) of the 111 syphilitic children after an average period of fifty-one and four-tenths months of postnatal observation, and of 100 (84 per cent) of the 119 children originally felt to be nonsyphilitic after an average follow-up period of fifty-five and one-tenth months. The subsequent discussion is concerned with the ultimate outcome in these two groups and with the accuracy of the initial diagnoses.

ULTIMATE OUTCOME OF THE INFANTS OF TWO HUNDRED AND THIRTY SYPHILITIC WOMEN

As analyzed in table 1, the known mortality rate among the group of syphilitic children was 32.4 per cent, as compared with 10.9 per cent among the apparently healthy offspring of syphilitic parents. There are no figures available on the mortality rate during the first five years of life of all children born at the Philadelphia General Hospital. The average age at death of the 13 syphilitic children who were discharged alive from the hospital was 7.2 months; only 1 was more than 1 year of age. Pneumonia was given as contributory to the primary cause of death of 5 of these infants. The average length of life of the children of the nonsyphilitic group who died after discharge from the hospital was 17.2 months. Causes of death are listed as pneumonia in 2 cases, diphtheria and neuroblastoma. In 2 instances the cause of death was not definitely determined, but there were no symptoms indicative of syphilis.

Infants of the supposedly nonsyphilitic group were subjected, so far as possible, to complete physical examination and to serologic tests of the blood with at least two, and sometimes with as many as five,

separate antigens, often in two separate laboratories, at the ages of 1 month, 2 months, 3 months, 6 months and 1 year and then yearly thereafter for the duration of the study. Studies of the spinal fluid were not performed in the absence of evidence of syphilis in other tests.

We feel that it is of especial significance in establishing the validity of the diagnostic methods employed in early infancy that not 1 baby of the 87 who were considered nonsyphilitic in the original series and who were subsequently followed for as long as six years showed any evidence of syphilis up to the time of his last examination. It seems safe to assume, therefore, that unless late congenital syphilis is discovered in members of this group at some subsequent date, adequate roentgenographic and serologic study in early infancy approached 100 per cent efficiency in the elimination of this disease.

TABLE 1.—*The Mortality Rate and Duration of the Postnatal Observation Period Among Infants (Classified in Accordance with Diagnosis Made in Infancy) of Two Hundred and Thirty Syphilitic Women (1933 to 1935 Series)*

Outcome	Syphilitic Group		Nonsyphilitic Group		Total	
	Number	Per Cent	Number	Per Cent	Number	Per Cent
Total mortality	36	32.4	13	10.9	49	21.3
Stillborn	16	14.4	5	4.2	21	9.1
Death within 24 hours	5	4.5	1	0.8	6	2.6
Death in nursery (2 to 14 days)	2	1.8	1	0.8	3	1.3
Death after discharge from hospital	13	11.7	6	5.1	19	8.3
Total alive at end of observation period	75	67.6	106	89.1	181	78.7
Followed less than 6 months	29	26.1	19	16.0	48	20.9
Followed 6 months to 6 (average 4.5) years	46	41.5	87	73.1	133	57.8

CRITICAL ANALYSIS OF THE GROUP OF INFANTS DIAGNOSED AS SYPHILITIC

While it gives a certain sense of assurance and satisfaction to know that the diagnostic methods employed are capable of detecting congenital syphilis with such accuracy at the time when treatment is most effective, in order to arrive at a fair analysis of the subject it seems desirable to determine if possible whether the procedures recommended are in any sense hyperacute. We have accordingly studied in some detail the 46 infants diagnosed as syphilitic and followed for an average of fifty-one and four-tenths months, as well as the 13 infants who died of complications of this disease after discharge from the hospital (table 2). In this group 18 (30.5 per cent) of the mothers had syphilis the duration of which was less than four years; 10 (17 per cent) were known to have had the disease more than four years, but in the majority, 31 (52.5 per cent), the disease was of unknown duration. What is more

important, however, is the fact that 17 (28.9 per cent) of these mothers received no prepartal treatment and that an additional 27 (45.9 per cent) received less than two months of arsenical therapy.

Perhaps the most striking revelation of table 2, aside from the indication that the mortality rate approaches zero for those infants who received active therapy for a year or more, is the fact that the offspring who were diagnosed as syphilitic in infancy only to remain untreated have fallen sharply into two categories on subsequent study: (*1*) those who died as a result of syphilis and (*2*) those who survived with no clinical or serologic evidence of the disease. It will also be noted that a large percentage of the infants diagnosed as syphilitic but subsequently treated inadequately, according to most accepted standards, likewise became clinically and serologically normal. The possibility of detecting any diagnostic error will arise largely from a study of these two groups

TABLE 2.—*Comparison of Status at the End of Observation of Fifty-Nine Infants Diagnosed as Syphilitic and Adequately Followed, as Compared with Amount of Postnatal Treatment for Congenital Syphilis (1933 to 1935 Series)*

Status of Infant	Postnatal Treatment		
	None	Inadequate (Average 8.4 Wk.)	More Than 1 Year of Active Therapy
1. Clinically and serologically cured	13	12	15
3. Still showing signs and symptoms of syphilis and/or positive serologic reaction of blood	..	3	3
3. Died as a result of syphilis	10	3	..
Total	23	18	18

of cases, since such an analysis is precluded in instances in which the infant has undergone adequate postnatal treatment.

Attention should be called to the fact that while it is the disposition assigned to the two groups of cases just mentioned that tends to color the ultimate results of any study which deals with the management of congenital syphilis, most previous writers have tended to avoid the issue as unimportant. They either have adopted more or less arbitrary standards of diagnosis, at times acceptable in their entirety only to themselves, or have excluded doubtful cases completely from the analysis, hoping that statistical averages in large groups of patients would tend to minimize this omission. McKelvey and Turner,[11] for instance, in one of the most carefully compiled analyses ever made on this subject, were compelled to resort to both of these devices. Thus, they presented a short summary of the methods employed in the pediatric follow-up

11. McKelvey, J. H., and Turner, T. B.: Syphilis and Pregnancy: An Analysis of the Outcome of Pregnancy in Nine Hundred and Forty-Three Cases, J. A. M. A. **102**:503 (Feb. 17) 1934.

study which, as they stated, "is of value chiefly from the standpoint of the normal group [of infants]," since, of course, the ultimate outcome of the group considered as syphilitic is not considered once the diagnosis of the disease has been established; and they excluded from consideration completely because of insufficient evidence to make a positive diagnosis approximately one third of all the infants, a group which included "cases in which clinical, pathological or roentgenologic evidence was questionable." Whipple and Dunham [12] and Black,[2b] in their recent critical reviews, pointed out many of the irreconcilable statements in the literature on infantile congenital syphilis which arise, in large part, from these often necessary, though self-imposed, standards. Black went so far as to suggest, with some apparent justification, that some of the statistical differences between the paper of McKelvey and Turner and the original (1935) report [1] of the present series might arise from differences in the handling of this group. Such a question, of course (as would probably be the case with many of the studies in this field), is one which the authors themselves might have difficulty in answering after careful comparative analysis of their respective material.

SPONTANEOUS REMISSION OF CONGENITAL SYPHILIS

An adequate study of these infants, improperly diagnosed or self "cured," as the case may be, is rendered difficult by a lack of knowledge of the frequency of spontaneous cure of congenital syphilis and of the temporary or permanent remission of clinical symptoms and disappearance of laboratory evidence after a short course of therapy. Such spontaneous remissions are known to occur in the adult with acquired syphilis, but the severity of the disease as one is apt to picture it in the untreated infected infant has largely precluded any such considerations when one thinks of the congenital infection. There has even been, at times, a tendency to attribute the rapidly favorable response of infantile congenital syphilis in some cases to inadequacy of diagnosis rather than to the effectiveness of treatment.

To approach the problem from the purely clinical standpoint, there are indications that "the blood Wassermann reaction ranks lower in the recognition of tardive heredosyphilis than it does in many other forms of syphilis and contrasts markedly with the 100% estimate of its value after the first two or three months of infancy" (Stokes [13]). Scattered throughout the literature on congenital syphilis are many statements implying the possibility of spontaneous cure. Thus, Black [2b] (1939) stated: "It is not improbable that congenital syphilis occasionally cures

12. Whipple, D. V., and Dunham, E. C.: Congenital Syphilis: I. Incidence. Transmission and Diagnosis, J. Pediat. **12**:386 (March) 1938.

13. Stokes, J. H.: Modern Clinical Syphilology, Philadelphia, W. B. Saunders Company, 1934, p. 1240.

itself." Nabarro[14] (1939) wrote: "It is possible that the infection [congenital syphilis] may be so slight that it is adequately dealt with and overcome by the natural defense mechanism of the growing child." Howard[15] (1939) gave recognition to the noteworthy response of some infants to small amounts of therapy with the remark, "Some children have a natural ability to overcome the infection with surprisingly little help." Jeans[16] (1937) stated: "Spontaneous recovery from [congenital] syphilis has been observed . . . sufficiently often to give assurance that it is one of the possible outcomes of this infection," and in one of his earlier works with Cooke[17] he described "twelve instances of such spontaneous recovery in children first seen during early infancy." (See also the work of Moore[18] and the report by Cole and his collaborators,[19] of the Cooperative Clinical Group, on the implied intrauterine cure of congenital syphilis.)

In this connection the studies of Smith[20] are also of interest, though deductions can be made only from inference, since he apparently did not study specifically the question of spontaneous "cure." Nonetheless, he was able to obtain 69.4 per cent of serologic cures among 43 infants, approximately 85 per cent of whom apparently had clinical as well as serologic evidence of syphilis from birth to 3 months of age but who received less than twelve injections of antisyphilitic drugs during the first year of life; 75.4 per cent of his syphilitic infants less than 2 years of age had negative serologic reactions with a total of less than thirty treatments (i. e., about six months of therapy).

Still further to clarify the problem with which we are confronted in our present series, we should like to present in considerable detail 2 representative cases, instances of apparently active infantile congenital syphilis in which the disease was clinically and serologically "cured," in the first instance after hyperpyrexia from an "intercurrent" infection and in the second after (and possibly as a result of) what most clinicians would consider grossly inadequate specific therapy.

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14. Nabarro, D. N.: Congenital Syphilis, Practitioner **142**:516 (April) 1939.

15. Howard, P. J.: Congenital Syphilis: A Ten Year Study of Forty-Five Children, J. Pediat. **14**:220 (Feb.) 1939.

16. Jeans, P. C.: Syphilis, in Brennemann, J.: Practice of Pediatrics, Hagerstown, Md., W. F. Prior Company, Inc., 1937, vol. 2, chap. 26, p. 44.

17. Jeans, P. C., and Cooke, J. V.: Prepubescent Syphilis, in Haynes, R. S.: Clinical Pediatrics, New York, D. Appleton and Company, 1930, vol. 17, chap. 12, p. 254.

18. Moore, J. E.: The Modern Treatment of Syphilis, Springfield, Ill., Charles C. Thomas, Publisher, 1933, p. 257.

19. Cole, H. N., and others: Syphilis in Mother and Child, Ven. Dis. Inform. 1940, supp. 7, p. 14.

20. Smith, F. R., Jr.: Congenital Syphilis in Children: Results of Treatment in Five Hundred and Twenty-One Patients, Am. J. Syph. & Neurol. **19**:532 (Oct.) 1935.

REPORT OF CASES

CASE 1.—*Apparent remission of congenital syphilis following hyperpyrexia associated with bronchopneumonia.*

L. D. J. was born on Dec. 14, 1934 as the issue of the first pregnancy of a 19 year old unmarried Negress with latent syphilis of unknown duration. Serologic tests of the mother's blood revealed the following results: diagnostic Kahn test 3 plus and cholesterolized Wassermann test 4 plus, on October 17; Kahn test 4 plus and cholesterolized Wassermann test 4 plus, on November 7. Prepartal treatment consisted of the administration of neoarsphenamine, 0.2 Gm. on November 7 and 0.3 Gm. on November 14. A serologic test of the maternal blood gave a strongly positive reaction at the time of delivery, and the cord blood serum gave a 1 plus reaction to a Kahn test and a 4 plus reaction to a cholesterolized Wassermann test. Dark field examination of the wall of the umbilical vein showed Spirochaeta pallida. A roentgenogram of the infant at the age of 6 days showed no evidence of congenital syphilis in the long bones. The infant weighed 6 pounds 4 ounces (2,835 Gm.) and was clinically normal at birth.

In view of the fact that we were at that time endeavoring to determine the diagnostic value of the dark field examination of the wall of the umbilical vein, this infant was not given treatment for syphilis but was observed periodically. He was again normal on routine physical examination on Jan. 7, 1935, and the result of a Kahn test of the blood serum was negative. He was brought to the clinic on January 15 because of a gastrointestinal disturbance and the passage of blood-streaked mucus. Physical examination at this time revealed some maceration and inflammation about the anal orifice. There was moderate obstruction to nasal breathing, with mucopurulent nasal discharge. The edge of the liver and the spleen were both palpable, and there was slight generalized lymphadenopathy, including the epitrochlear glands. The blood showed a 4 plus Kahn reaction and a 4 plus cholesterolized Wassermann reaction, and a roentgenogram of the long bones revealed thin, irregular lines of increased density in the temporary zones of calcification of the distal metaphyses of the radiuses, ulnas, femurs and tibias and subjacent areas of submetaphysial rarefaction which strongly suggested congenital syphilis.

The infant was not seen again until he was admitted to the hospital with confluent bronchopneumonia, on February 11. The temperature was elevated to 105 F. and maintained an irregularly elevated course for the next week, with a total of eighty-one hours over 102 F. Treatment for syphilis was withheld during the acute phase of his illness and was not commenced subsequently, when blood drawn for serologic tests on February 19, the first day following the return of the temperature to normal, was reported as giving negative reactions to a Kahn test and to a cholesterolized Wassermann test. In spite of this fact, the roentgenograms of the long bones made on the same day showed progression of the skeletal lesion previously described, with widening and increased irregularity of the bands of sclerosis in the distal metaphyses and of the bands of submetaphysial rarefaction and the development of early periostitis on the shafts of the radiuses, ulnas and femurs. The infant was discharged on February 28.

On the infant's return to the outpatient department, on March 5, the only evidence of the acute infection was persistence of the nasal discharge and cough. The generalized lymphadenopathy and the palpability of the liver and spleen persisted. A roentgenogram of the long bones at this time indicated that the skeletal changes described were stationary; a repetition of the study, made on June 18, showed complete healing of the osseous lesions. Unfortunately, sero-

logic tests of the blood were not repeated until August 13, when the Kahn reaction was again negative. A Kahn reaction was negative on Jan. 26, 1937, and Kahn and Kolmer-Wassermann reactions were both negative on Oct. 24, 1939, the date of the last visit, at which time complete physical examination revealed no evidence of syphilis, in spite of the fact that the child had received no antisyphilitic chemotherapy.

CASE 2.—*Apparent cure of congenital syphilis with less than three months' therapy irregularly administered (associated with a febrile episode diagnosed as bronchopneumonia).*

The mother of H. D. was a 20 year old married Negress in whom papular lesions of the extremities, neck and thorax had developed, associated with a positive serologic reaction of the blood for syphilis two years prior to her present, which was her first, pregnancy. She received ten intravenous and ten intramuscular injections from a private physician at the time of onset of her disease and then disappeared from medical observation until the sixth month of her pregnancy, when physical examination revealed nothing abnormal and a Kahn test of her blood serum gave a negative result. No prepartal treatment for syphilis was given, and a Kahn test of blood serum from the cord gave a negative reaction at the time of delivery, on June 24, 1934.

The infant presented the following clinical evidence of syphilis when brought by the mother to the pediatric clinic, at the age of 3 months (September 17): (1) dactylitis, which had been present since the age of 6 weeks; (2) two discrete annulopapular lesions of the face; (3) a large, firm spleen palpable 4 cm. below the costal margin and a liver edge palpable 6 cm. below the ribs; (4) definite obstruction to nasal breathing, and (5) generalized lymphadenopathy, including the epitrochlear, inguinal, axillary and cervical nodes. A Kahn test of the infant's blood serum revealed a 4 plus reaction, and a cholesterolized Wassermann test, a 4 plus reaction, confirmed on repetition, and a serologic test of the maternal blood performed on September 25, likewise gave strongly positive results. A roentgenogram showed osteochondritic and periosteal changes of all the long bones, unequivocally diagnosed by the roentgenologist as indicative of congenital syphilis. Treatment, started on September 25, consisted of eight injections of bismuth subsalicylate (totaling 180 mg. of bismuth) up to December 11. The child then disappeared from observation until Feb. 5, 1935, when he was returned to the clinic as acutely ill and was admitted to the ward with what was termed bronchopneumonia. The temperature, however, which never exceeded 103 F., returned to normal within forty-eight hours. On February 5 the result of a Kahn test was 4 plus and that of a cholesterolized Wassermann test 4 plus. Hospitalization was continued for the next month, during which time he received four injections of sulfarsphenamine (totaling 0.6 Gm.) and concurrently four injections of bismuth subsalicylate (totaling 120 mg. of bismuth). Serologic tests of the blood gave only weakly positive reactions on March 20 (cholesterolized Wassermann and Kahn), and the spinal fluid was completely normal. He received no treatment after discharge from the hospital, but physical examination on July 25, 1939 (at the age of 49 months) showed no abnormality, and negative Kolmer-Wassermann and Kahn reactions were reported in two separate laboratories.

In considering the factors which might account for spontaneous remission of early congenital syphilis, one of the first that comes to mind is hyperpyrexia. Congenital syphilis in itself is known to be one of the causes of persistent low grade fever in infancy, possibly the result

of an associated chronic mild intercurrent infection in a person with lowered resistance, possibly one of the manifestations of the immunologic response of the infant to its syphilis. Four babies, in addition to the one cited, falling in the category of those "clinically and serologically cured without treatment," are definitely known to have had prolonged attacks of high temperatures within the first six months of life, one as the result of bronchopneumonia, another from Ludwig's angina, the third from persistent severe gastroenteritis and the fourth for some unexplained reason. The erratic temperature response of infants to what seems to be relatively minor infections is well known. How many infants in this series experienced episodes similar to those just described it is impossible to state.

Syphilitic infants with positive reactions to serologic tests at birth which revert to negative and then return to positive at some future date have been observed by us on other occasions [21] (table 5) and have been reported by various authors.[22] During the period in which the original study was performed, with the serologic technics then employed, the syphilitic reagin transferred from the maternal blood stream was seldom seen to persist in the infant's blood stream beyond two weeks postnatally (see also Cregor and Dalton [23]). The irregular (so-called saw tooth) appearance of the metaphysial densities is considered by most writers, even in the light of recent studies, as characteristic of congenital syphilis,[24] and we have not seen periosteal changes from rickets develop in the infant with congenital syphilis earlier than two and one-half to three months postnatally. This is apparently in accord with Caffey's [5] observations and with the recently reported experience of Evans.[7] We have not encountered traumatic periostitis of the newborn or periostitis developing from other unusual conditions (e. g., that associated with erythroblastosis or gonorrhea) in this group. These observations would seem to minimize the possibility of faulty diagnosis through misinterpretation of the serologic reactions of the blood or roentgenographic findings in case 1.

ROENTGENOGRAPHIC INTERPRETATION

This portion of the reevaluation seemed particularly worth while because of the completeness of the original studies in this regard. Seventy-eight (89 per cent) of the 88 infants who were discharged

21. Ingraham, N. R., Jr.: Roentgen Positive Seronegative Infantile Congenital Syphilis, Am. J. Dis. Child. **50**:1444 (Dec.) 1935.

22. Bridgeman, M. L.: Diagnosis of Syphilis in the Neonatal Period, Northwest Med. **38**:389 (Oct.) 1939. Christie.[8] Davies.[4]

23. Cregor, F. W., and Dalton, J. E.: Syphilotoxemia in the New-Born, Arch. Dermat. & Syph. **35**:580 (April) 1937.

24. Park, E. A., and Jackson, D. A.: The Irregular Extensions of the End of the Shaft in the X-Ray Photograph in Congenital Syphilis with Pertinent Observations, J. Pediat. **13**:748 (Nov.) 1938. Black.[2b] Caffey.[5]

alive from the hospital and were diagnosed as syphilitic and 85 (76 per cent) of the 112 infants diagnosed as nonsyphilitic were subjected to roentgenologic examination, and in a number of instances to serial studies, so that a total of about 250 separate roentgenographic investigations were performed (table 3).

In reviewing the data in table 2 on infants apparently clinically and serologically cured of their disease after no treatment or grossly inadequate treatment, we find a well substantiated initial diagnosis, similar to those in the cases reported, in all except 6, in whom treatment was commenced or a positive diagnosis established on roentgenographic evidence alone. These were all infants in whom the roentgenogram revealed the beginnings of periostitis between the ages of 2 and 5 months (average 3.3 months). It must be remarked, at this point, that it was

TABLE 3.—*Accuracy of Roentgenographic Diagnosis in Syphilitic and Nonsyphilitic Infants at Various Ages (1933 to 1935 Series)*

Age of Infant	Total Number of Roentgenograms in Each Age Period	Syphilitic Infants			Nonsyphilitic Infants		
		Roentgenogram		Per Cent Positive	Roentgenogram		Per Cent Positive
		Positive	Negative		Positive	Negative	
1 to 14 days	127	29	32	48	8	58	12
15 days to 8 weeks	38	28	2	93	1	7	13
9 to 16 weeks	62	28	0	100	4	30	12
Over 16 weeks *	30	10	2	83	1	17	6
Total	257	95	36		14	112	

* In the group over 16 weeks old, the average age of syphilitic infants was 34.5 weeks and that of nonsyphilitic infants 26.6 weeks.

not the purpose of the original (1935) study to examine critically the diagnostic methods employed. For the most part, the roentgenographic changes which had been described as syphilitic in origin were accepted as such without reserve. It was, of course, easier to check errors in the interpretation of osteochondritis in the immediate neonatal period than it was to restudy the changes which occurred at a later date. Periostitis at the age of 2 to 3 months was considered especially characteristic of congenital syphilis, and active rickets, recognizable as such, was rarely seen prior to the twentieth postnatal week (see also Evans [7]) in the type of children concerned in the study. Subsequent experience with serial roentgenographic studies has shown that periostitis in the negatively reacting offspring of a syphilitic mother is more apt to develop into frank rickets than into advanced infantile syphilis of the bone. We agree entirely with the opinions summarized by Black [2b] to the effect that the existence of unequivocal osseous syphilis roentgenographically demonstrable in the presence of negative serologic reactions when the better serologic technics are employed is extremely uncommon in early

infancy. Its occasional occurrence seems difficult to refute, however, in the light of observations like those of McCord,[25] in which not only the abnormal roentgenogram but S. pallida as well was demonstrable in 7 infants with negative results to serologic tests.

The observations just described have led us to review completely our series to determine the approximate accuracy of roentgenographic diagnosis at the various age periods of early infancy (table 3). Supplementary roentgenographic diagnosis of infantile congenital syphilis is accordingly seen to be of some value in all the age periods studied. Early diagnostic errors (before the age of 2 months) usually arose either from too close reading of roentgenograms, which tended to place too much significance on minor changes without an adequate knowledge of so-called normal variations, or from misinterpretation of the densities produced by antenatal therapy. Later diagnostic errors (i. e., after the age of 2 months) from the roentgenographic standpoint resulted almost invariably from confusion caused by the periosteal changes often associated with developing rickets. It is to be remembered that the summary contained in table 3 is of a period five to seven years previous to the time of writing and that it concerns a diagnostic field in which basic knowledge is steadily progressing.

RELATIVE IMPORTANCE OF THE VARIOUS DIAGNOSTIC AIDS EMPLOYED FOR DETECTING INFANTILE CONGENITAL SYPHILIS

In order to determine what can be expected from roentgenographic and serologic diagnosis of infantile congenital syphilis at present and to determine the practical importance of the recent advances in these fields so far as the conduct of an active congenital syphilis clinic is concerned, we have prepared for comparison with the foregoing studies an analysis of the results we obtained in this field at the Philadelphia General Hospital from September 1938 to January 1940 inclusive. During this sixteen month period 220 syphilitic women were delivered, with 25 stillbirths or neonatal deaths. The average age of the syphilitic mothers was 23 years, and approximately 80 per cent were colored. The excellence of our present follow-up service made it possible for us to follow periodically 93 of the 195 living offspring for more than one year and 162 for six months or longer. In tables 4, 5 and 6 no case of a nonsyphilitic infant has been included who has not been followed by means of physical examinations and serologic studies for at least six months postnatally.

In the examination of these tables, it becomes at once apparent that while the roentgenogram has been used somewhat less frequently for

25. McCord, J. R.: Syphilis in the Pregnant Woman, Surg., Gynec. & Obst. **66**:441 (Feb., no. 2A) 1938.

TABLE 4.—*Roentgenographic Diagnosis in Infants Selected from One Hundred and Sixty-Two of Those Born of Syphilitic Mothers from September 1938 to January 1940*

Age of Infant	Total Number of Roentgenograms in Each Age Period	Syphilitic Infants			Nonsyphilitic Infants *		
		Roentgenogram		Per Cent Positive	Roentgenogram		Per Cent Positive
		Positive	Negative		Positive	Negative	
1 to 14 days	64	5	3	63	0	56	0
15 days to 2 months	37	6	0	100	0	31	0
2 to 4 months	23	6	0	100	1	16	5
Over 4 months	None	None			None		
Total	124	17	3		1	103	

* Infants considered nonsyphilitic only after a minimum observation period of six months.

TABLE 5.—*Maternal-Infant Serologic Status in One Hundred and Seven Syphilitic Deliveries at the Philadelphia General Hospital Between September 1938 and January 1940, Illustrating the Statistical Significance of Each Possible Combination in an Active Syphilis Service*

Type	Number	Per Cent of Total
1. Nonsyphilitic infants *		
(*a*) Maternal Wassermann reaction positive; infant's Wassermann reaction positive at birth, reverting to negative postnatally	19	17.6
(*b*) Maternal Wassermann reaction positive; infant's Wassermann reaction negative at birth	48	45.4
(*c*) Maternal and infant's Wassermann reactions negative at birth	30	27.8
2. Syphilitic infants		
(*d*) Maternal and infant's Wassermann reactions positive at birth	7	6.5
(1) Infant's titer remaining positive and increasing	(5)	(4.7)
(2) Infant's titer decreasing to negative or nearly so, only to increase again at later date	(1)	(0.9)
(*e*) Titer of infant's Wassermann reaction significantly greater than titer of mother at birth	(1)	(0.9)
(*f*) Maternal Wassermann reaction positive; infant's Wassermann reaction negative at birth, becoming positive at varying periods postnatally	3	2.7
(*g*) Maternal and infant's Wassermann reaction negative at birth, infant's subsequently becoming positive	—	0.0
Total	107	100.0

* Nonsyphilitic infants followed at least six months postnatally. Amount of prepartal treatment and duration of disease in the mother not held constant.

TABLE 6.—*Diagnostic Value of a Positive or Negative Serologic Reaction of the Blood for Syphilis in Various Age Groups from Birth to 1 Year (1938 to 1940 Series)*

Age of Infant	Syphilitic Infants			Nonsyphilitic Infants †		
	Serologic Reaction		Per Cent Positive	Serologic Reaction		Per Cent Positive
	Positive *	Negative		Positive	Negative	
(1) Birth to 10 days	7	4	64	20	103	16.2
(2) 11 days to 1 month	6	3	67	9	125	6.7
(3) 1 to 2 months	2	3	40	3	87	3.3
(4) 2 to 3 months	3	0	100	0	122	0.0
(5) 3 to 6 months	4	0	100	0	153	0.0
(6) 6 months to 1 year	..	..	...	0	93	0.0

* Positive serologic reactions of syphilitic infants were not recorded after commencement of therapy.

† All nonsyphilitic infants (with negative serologic reactions) were followed at least six months postnatally. Prepartal treatment and duration of disease in mother were not held constant.

diagnostic purposes, its accuracy has, if anything, improved. This has resulted in large part from reluctance to consider anything but advanced osseous changes as indicative of congenital syphilis and from improvement in our knowledge of the effect of prenatal treatment in causing bone densities. As a result, the misinterpretations in the neonatal period, in this short series at least, have disappeared, and the sole discrepancy in the two to four month period, in the case of a 2½ month old infant with negative results to serologic tests, resulted from again interpreting early rickets, which subsequent roentgenograms showed in its true light, as congenital osseous syphilis.

Fortunately, the various conditions which Caffey [5] has so admirably described as confusing the diagnosis of syphilitic osteochondritis (erythroblastosis, familial hemolytic anemia, congenital atresia of the common bile duct and the various forms of bacteremia, such as pneumococcic, septic hemolytic and tuberculous) are sufficiently uncommon that they have not been encountered in the period of this study among the offspring of syphilitic mothers during the first few weeks of life. For accurate interpretation of the roentgenogram it is, in our experience, critically essential that the roentgenologist consider, in addition to the general physical status of the infant and the amount and duration of heavy metal therapy given to the mother prepartally, the exact age of the infant being studied. We emphasize this last point in particular because in the majority of instances by the time an infant with congenital syphilis, who of course has usually been infected some days or weeks prior to delivery, reaches the age of 6 weeks there can be little doubt as to the nature of the osteochondritic changes, while most of the other conditions to be confused with it develop at a somewhat later period and at this more advanced age show a type of early osteochondritic change that is usually demonstrable in congenital syphilis during the first month of life. Thus, when from Caffey's [5] series of 15 instances of for the most part relatively infrequently encountered early osteochondritic changes simulating congenital syphilis the 2 cases of bismuth osteopathy (which fall in a separate category) are excluded, 8 of the remaining 13 infants fall in the 6 week to 4 month age period (average 2.5 months), in which this type of early change as a result of congenital syphilis is unlikely.

While on the subject of the roentgenographic demonstration of congenital osseous syphilis, we should like again to say a word in opposition to the employment of this method as a routine diagnostic procedure for all offspring of syphilitic parentage, as is done apparently in many institutions. However praiseworthy such an effort may be from the research standpoint, it is of relatively little practical value and does not justify the expense. The reason for this is that in any obstetric practice which boasts even an approximation to adequate treatment of the

syphilitic expectant mother the incidence of syphilis among the offspring is so low that routine roentgenographic examination will be employed to identify syphilis in only 1 of perhaps 4 to 8 normal offspring. In the present study, for instance, the roentgenogram was found to be of some positive diagnostic value in 10 (27 per cent) of the instances in which the mother had had no prepartal treatment, in 5 (10 per cent) of the cases in which she had less than two months of prepartal therapy but in no instance in which as much as sixteen weeks of prepartal treatment had been administered.

It is also important to note that the failure to consider such factors as the adequacy and type of prepartal therapy and the duration and activity of the disease in the mother undoubtedly accounts in large part for the variations found in the literature in the percentage of roentgenograms with positive signs during the first two weeks of postnatal life. Thus, in contradistinction to the 48 and 63 per cent, respectively, of positive roentgenograms in the two series here reported, Christie [9] was able to detect only two in 15 cases of syphilis (14.4 per cent) during the neonatal period, at a time when the diagnostic roentgenologic error was 1.5 per cent (1 positive diagnosis among 68 nonsyphilitic infants). McKelvey and Turner,[11] working at an earlier period in the same institution, found that the roentgenograms of 19 (30.7 per cent) of 62 syphilitic infants were positive during the same period (first two weeks of postnatal life). All 19 of these infants "eventually presented supporting evidence for the diagnosis of syphilis." The roentgenogram of the long bones serves its chief value as a subsidiary diagnostic aid during the first few weeks of postnatal life in differentiating between the syphilitic and the nonsyphilitic positively reacting offspring of the untreated or inadequately treated syphilitic pregnant woman.

Table 3 shows the relative frequency of the various serologic combinations encountered during the sixteen month period of this study. The quantitative titered Wassermann test [26] was of value in assisting in the study of approximately one fourth of the offspring of syphilitic parentage encountered during this period. Table 6 shows that of 27 infants with positive serologic reactions of the blood at the time of birth, 20 (74 per cent) did not have syphilis. More than half of these infants had negative serologic reactions by the age of 1 month, but about 3 per cent of the nonsyphilitic infants presented a positive serologic reaction persisting into the second month of postnatal life. We feel that the persistence of syphilitic reagin in the nonsyphilitic infant's blood stream for an apparently longer period postnatally in the present series

26. The quantitative titered Kolmer-Wassermann tests for this study were performed by Miss Verna Mayer, of the laboratory of the Syphilis Clinic, Hospital of the University of Pennsylvania.

as compared with that in the 1933 to 1935 series probably results from some increase in sensitiveness of the serologic technics employed from 1938 to 1940. In the sole instance in which the reagin titer of the infant's serum was considered to be significantly greater than that of the mother's at birth (table 3, type *2e*) the mother's serum contained 8 units and the infant's 64 units (both titrations being performed on the same day in the same laboratory). The fact that no mother with a negative serologic reaction gave birth to a syphilitic infant (table 5, type *2g*) during one and one-third years indicates the relative infrequency of this occurrence, at least when some prepartal treatment is given. We have included such a classification in the table, however, since such cases are known to exist and we have encountered an occasional example (see also Stokes and Ingraham [27]). We have likewise observed in several instances, as did Davies,[4b] a temporary slight rise in the serum reagin titer of a nonsyphilitic infant, but since this finding has been inconstant we have been inclined to consider it as a possible indication of daily fluctuations in the sensitiveness of the tests employed, as suggested by the work of Mohr and Smith.[28]

In the brief period in which we have had the opportunity to apply the quantitative titered Wassermann test routinely, we have been impressed with the fact that it has considerably greater value in eliminating the nonsyphilitic patient with positive serologic reactions, by detecting a rapidly falling titer, than it has in establishing an absolute diagnosis in the study of the truly syphilitic patient. Our experience has been somewhat in accord with Christie's,[8] in that syphilitic infants with positive serologic reactions at birth seldom seem to show a rapid or significant increase in the titer short of an observation period of one month or six weeks. It will be noted that in the first of Christie's 3 cases, the titer commenced to rise between four and six weeks postnatally and in the third between six and seven weeks, while in the second no serologic tests were performed between four days and two months after birth.

Our observation, further, does not completely corroborate Black's statement [2b] to the effect that a delay in diagnosis immediately after birth of from six weeks to two months is not harmful to the infant in some cases. Two babies in the present series, each with a reagin titer fluctuating between 8 and 16 units on weekly determinations, died at

27. Stokes, J. H., and Ingraham, N. R., Jr.: Diagnosis and Treatment of Congenital or Prenatal Syphilis [case 2], M. Clin. North America **23**:1575 (Nov.) 1939.

28. Mohr, C. F., and Smith, C. A.: On the Supposed Daily Variation of the Reagin Content of Syphilitic Serum, Am. J. Syph., Gonor. & Ven. Dis. **24**:322 (May) 1940.

the age of 16 and 25 days, respectively, while awaiting adequate serologic diagnosis. Both of these infants, though presenting no diagnostic or suggestive lesions of the skin or mucous membranes, had both roentgenologic and autopsy evidence of syphilis. It will remain uncertain, of course, whether the immediate institution of specific therapy would have saved either of these infants, and we realize that some clinicians feel that it probably would have been ineffectual (Aries [6] and Levin [29]); but we have occasionally encountered similar cases in which treatment judiciously administered has resulted in recovery. While one is waiting for a four to eight week postnatal period to determine the significance of a positive result to a serologic test by serial titrations, another roentgenogram of the long bones, after two or three weeks (at times even less), will often serve to clarify a previously doubtful roentgenographic interpretation and, likewise, suffice to corroborate a diagnosis of congenital syphilis.

SUMMARY AND CONCLUSIONS

A five year follow-up study of 230 infant offspring of syphilitic mothers born at the Philadelphia General Hospital during the eighteen months from October 1933 to April 1935 is presented for the purpose of determining the accuracy of the diagnostic methods employed for the detection of infantile congenital syphilis in the light of recent advances in the knowledge of serologic and roentgenographic interpretation.

Approximately one third of the syphilitic group are known to have died, as compared with one tenth of the nonsyphilitic group, but it has been possible to reexamine about 70 per cent of the remaining living children after four to five years.

It is considered significant that no infant was discovered in whom serologic tests and the roentgenographic procedures employed had not been able to establish the diagnosis of syphilis in infancy, if it was present.

The spontaneous remission of clinical symptoms and the disappearance of laboratory evidence of the disease after comparatively little or, at times, no antisyphilitic treatment may be a relatively frequent occurrence among the syphilitic infants who survive the first few months of their disease. Hyperpyrexia from an intercurrent infection may be one of the factors which bring about this apparent "cure."

Recent advances in the knowledge of interpreting the roentgenogram of the long bones in infancy have greatly increased the value of the procedure as a diagnostic aid for congenital syphilis. Misinterpretation of the roentgenogram, which introduced errors as great as 12 per cent five years ago, is becoming uncommon, largely through a

29. Levin, I. M., in discussion on Aries.[6]

better understanding of (1) the occurrence of rather wide variations in normal metaphysial densities, (2) the effect of prepartal treatment of the mother, with heavy metals in producing opaque shadows in the shafts of the infant's bones and (3) the importance of differentiating the early osteochondritic and periosteal changes developing in the malnourished rachitic infant 2 to 3 months of age. Other causes of diagnostic error have been infrequent in our experience.

Significant roentgenographic changes as a result of syphilis in an infant with negative serologic reactions of the blood are likewise unusual.

It is suggested that the use of the roentgenogram as a subsidiary diagnostic aid will be found of greatest value when it is reserved for the study of those infants in whom a recent infection of the mother or grossly insufficient amounts of prepartal treatment render the presence of the disease in the offspring most likely.

The quantitative titered Wassermann test seems to have its greatest value in detecting nonsyphilitic infants with positive serologic reactions at birth. In the present series 74 per cent of the infants presenting positive serologic reactions during the immediate neonatal period (up to fourteen days postnatally) apparently did not have syphilis.

The detection of the syphilitic infant by the use of the quantitative titered Wassermann test alone is complicated by the facts that, first, the birth of a syphilitic infant in whom the serum reagin titer is significantly greater than that of the mother is apparently an infrequent occurrence; second, the syphilitic as well as the nonsyphilitic infant may occasionally exhibit initially a decreasing titer, and, third, a significant rise in the serum reagin content may not occur for from four to eight weeks postnatally.

The most accurate diagnosis of infantile congenital syphilis would still seem to call for a close coordination in the interpretation of serologic reactions of the blood and roentgenographic changes.

ACTION OF DIHYDROTACHYSTEROL IN CHRONIC PEMPHIGUS

WALTER F. LEVER, M.D.
AND
JOHN H. TALBOTT, M.D.
BOSTON

The use of dihydrotachysterol in the treatment of pemphigus was suggested as the result of three observations: (*a*) the beneficial effects occasionally observed in pemphigus from the administration of large amounts of viosterol, (*b*) the improvement induced by the administration of dihydrotachysterol in impetigo herpetiformis and (*c*) the serum calcium–raising property of dihydrotachysterol.

Ludy and DeValin [1] in 1932 reported symptomatic improvement in 6 patients treated with large quantities of viosterol and with ultraviolet radiation. This observation has been confirmed by Tauber and Clarke,[2] by King and Hamilton [3] and by us (unpublished data). Although the precise mode of action in pemphigus of massive doses of viosterol (100,000 to 500,000 U. S. P. units of vitamin D per day) is not known, it seems unlikely that it is the correction of an avitaminosis D, as Ludy and Drant [4] assumed. If this explanation were valid, small amounts of viosterol would be expected to produce some clinical improvement. This has not been reported by others, nor have we observed any benefit in patients with pemphigus from the daily ingestion of from 5,000 to 10,000 units of vitamin D. A more reasonable explanation is to attribute the improvement to the serum calcium–raising property (calcinosis factor). Since dihydrotachysterol contains the calcinosis factor in higher concentration than viosterol, it appeared to us to be desirable to investigate the

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From the medical and dermatologic clinics of the Massachusetts General Hospital and the Fatigue Laboratory, Harvard University.

1. Ludy, J. B., and DeValin, C. M.: Viosterol in the Treatment of Pemphigus, Urol. & Cutan. Rev. **36**:817, 1932.

2. Tauber, E. B., and Clarke, G. E.: Treatment of Pemphigus with Concentrated Viosterol, Arch. Dermat. & Syph. **40**:82 (July) 1939.

3. King, H., and Hamilton, C. M.: Pemphigus Controlled by Vitamin D, Arch. Dermat. & Syph. **39**:515 (March) 1939.

4. Ludy, J., and Drant, P.: Concerning the Treatment of Pemphigus, with Report of Cases, Urol. & Cutan. Rev. **40**:105, 1936.

use of this substance by patients with pemphigus. Secondly, clinical improvement has followed the ingestion of dihydrotachysterol by patients with impetigo herpetiformis,[5] a disease similar in objective manifestations and clinical course of pemphigus. Since the drug was beneficial in impetigo herpetiformis, a trial in pemphigus seemed indicated. The third reason for giving dihydrotachysterol was the anticipated correction of the low calcium concentration in the serum observed in many patients with chronic pemphigus.[6]

In this communication case reports of 10 patients with pemphigus will be presented. These patients were all cared for in the dermatologic ward and were under the observation and control of the various dermatologists of the staff who happened to be in charge for the particular months when the patients were in the hospital. The condition in these cases represented the chronic type of pemphigus, which is usually not rapidly fatal but tends to have a protracted and debilitating course, in contrast to the acute type, which usually occurs in persons of Jewish extraction, involves the mucous membrane of the mouth as well as the skin and runs an acute fulminating course. A diagnosis of pemphigus vulgaris was made in most of these cases.

Several aspects of the metabolic disturbance in pemphigus previously reported [6] were confirmed. A reduction in concentration of serum protein and sodium as well as of calcium was observed. An increase in volume of plasma and interstitial fluid was noted in most of the patients who were studied. Ingestion of dihydrotachysterol restored the concentration of the chemical constituents but did not change the altered volumes of body fluids.

Clinical improvement followed the chemical restoration induced by dihydrotachysterol in each patient. Several experienced a relapse when administration of the drug was discontinued. Resumption of treatment was followed again by improvement. Two patients in this series died, one from pemphigus complicated by bronchopneumonia six weeks after cessation of treatment with dihydrotachysterol, and the other from a cerebral accident. The remaining 8 patients are alive and active and have few or no lesions of pemphigus at the time of writing. Four of them have been essentially symptom free for more than a year. The others have been treated for a shorter period, but improvement has been equally encouraging. In addition to the foregoing patients, 2 others will be discussed briefly. They were 80 and 78 years old, respectively. Both

5. Schubert, M.: Impetigo herpetiformis, ihre Behandlung mit A.T. 10, Dermat. Wchnschr. **102**:761, 1936. Bartmann, J.: Zur ätiologischen Therapie der Impetigo herpetiformis, Arch. f. Dermat. u. Syph. **175**:93, 1937.

6. Talbott, J. H.; Lever, W. F., and Consolazio, W. V.: Metabolic Studies on Patients with Pemphigus, J. Invest. Dermat. **3**:31, 1940.

were acutely ill on admission, were given dihydrotachysterol for only a short time and died while under treatment. It is believed by us that the drug contributed to their death and that it should be used with great caution by elderly people and by those with renal impairment.

METHODS

The methods for the analysis of the chemical constituents of the blood have been described.[7] Blood and plasma volumes were determined with the photocolorimeter by the method of Gibson and Evans.[8] Interstitial fluid volumes were determined by the method of Crandall and Anderson.[9] The concentrations of total base, sodium, potassium and calcium in the serum will be expressed in milliequivalents per liter. Protein will be expressed in grams per hundred cubic centimeters and phosphate and nonprotein nitrogen in milligrams per hundred cubic centimeters. The following average range for normal was determined in our laboratory: total fixed base 150 to 155, sodium 139 to 141, potassium 4 to 5, calcium 4.7 to 5.4 and chloride 102 to 106 milliequivalents per liter; protein 6.4 to 7.5 Gm.; phosphate 3.1 to 4.5 mg. and nonprotein nitrogen 20 to 34 mg., per hundred cubic centimeters. The average body fluid volumes for normal subjects are: plasma volume, 45 cc. per kilogram, and interstitial fluid volume, 20 per cent of body weight.

REPORT OF CASES

CASE 1.—E. H., a 74 year old Swedish-born man, was admitted to the hospital with a severe generalized bullous eruption of five months' duration. The clinical diagnosis was chronic pemphigus. During the first three weeks in the hospital his condition became steadily worse. On Dec. 10, 1937 treatment with dihydrotachysterol[10] was begun. A dose of 5 cc. was given daily for nine days. In addition he received 6 Gm. of calcium gluconate by mouth each day. Improvement was noted within a week after institution of this regimen. Ten days later the appearance of new lesions had ceased, and after two and one-half weeks all of the lesions had healed. During this course of treatment the concentration of calcium in the serum had increased from 4.3 to 6 milliequivalents per liter. Twelve days after the administration of dihydrotachysterol had been discontinued new lesions appeared. The calcium had decreased to 5 milliequivalents per liter. Within one week new bullae covered large areas of the body. The administration of dihydrotachysterol

7. Talbott, J. H.: The Interpretation of Clinical Chemical Procedures. Ohio State M. J. **35**:137, 1939.

8. Gibson, J. G., Jr., and Evans, W. A., Jr.: Clinical Studies of the Blood Volume: I. Clinical Application of a Method Employing the Azo Dye "Evans Blue" and the Spectrophotometer, J. Clin. Investigation **16**:301, 1937.

9. Crandall, L. A., Jr., and Anderson, M. X.: Estimation of the State of Hydration of the Body by the Amount of Water Available for the Solution of Sodium Thiocyanate, Am. J. Digest. Dis. & Nutrition **1**:126, 1934.

10. The preparation of dihydrotachysterol used in this study was A. T. 10, a 0.5 per cent solution in sesame oil. It was administered orally.

was resumed for twelve days; 5 cc. was given daily. Again the skin became free of lesions within twenty days, and the calcium concentration increased to 7 milliequivalents per liter. The serum protein, which was 5.4 Gm. on admission, was 7.4 Gm. per hundred cubic centimeters at this time. During the last two days of this period, the patient experienced some nausea and appeared stuporous. These symptoms were interpreted as early signs of hypercalcemia. The patient left the hospital in good condition. Treatment was not continued, however, and the cutaneous lesions returned. He died one month after discharge in his local hospital from pemphigus complicated by bronchopneumonia without having received any treatment with dihydrotachysterol in the interval.

CASE 2.—E. H., a 74 year old German-born man, was admitted to the hospital with a generalized bullous eruption of four months' duration. The clinical diagnosis was chronic pemphigus. The results of two Pels-Macht tests, two months apart, were 62 and 64 per cent. On Dec. 13, 1937 treatment with dihydrotachysterol was begun. A daily dose of 5 cc. was given for fifteen days. Improvement was noted within seven days, and before cessation of treatment the lesions had cleared completely. The serum calcium had increased from 4.4 to 5.5 milliequivalents per liter and the serum protein from 5.4 to 7.6 Gm. per hundred cubic centimeters. Nine days after discharge a relapse became apparent. Within three weeks he had many bullous lesions, and the administration of dihydrotachysterol was resumed, with the same dose for nine days. Seven days after the resumption the lesions began to regress. The skin was free of lesions one week later. The serum calcium, which had decreased to 5.1 milliequivalents per liter after the first course of treatment, rose to 5.6 milliequivalents, and the protein increased to 8.1 Gm. per hundred cubic centimeters, an increase of 2.7 Gm. over the initial level. The calcium was maintained at a level of approximately 6 milliequivalents per liter during the following three weeks by administering 5 cc. of dihydrotachysterol every third day. The patient meanwhile remained free of symptoms. He died suddenly, from a cerebral accident. This was the third cerebral episode that he had had during twelve months. It seems unlikely that the use of dihydrotachysterol contributed to the terminal accident.

CASE 3.— D. F., a 19 year old American woman, was admitted to the hospital with a generalized bullous eruption of one month's duration. She was in her sixth month of pregnancy. The clinical picture was typical of pemphigus, but because of the coexistance of pregnancy, the diagnosis of pemphigoid eruption of pregnancy was made. The result of a Pels-Macht test was 66 per cent. A course of treatment with dihydrotachysterol was begun, and 5 cc. was given daily for thirty-one days. By the end of the fourth week healing of the lesions was observed. The skin was free of lesions by the end of the seventh week, and she was discharged a few days later. She remained at home only one week before new lesions appeared. On reentry to the hospital she had vesicles on the arms and legs. She was given 1 Gm. of calcium gluconate intravenously daily for three days and 6 Gm. of calcium gluconate by mouth with 2 cc. of viosterol in oil [10a] thereafter. The eruption disappeared within a week, and she was discharged. Three weeks after discharge she experienced a normal delivery. The baby was well and healthy. Two days after delivery a few papulovesicular lesions appeared on the hands and legs. These cleared rapidly, and the skin was in excellent condition at the last follow-up visit, fourteen months after delivery.

10a. Viosterol in oil N. N. R., containing 10,000 U. S. P. units of vitamin D per gram, was the preparation used in all the cases reported.

On admission the concentration of serum calcium was 4 and that of serum sodium 136 milliequivalents per liter and that of serum protein was 5.3 Gm. per hundred cubic centimeters. During treatment the calcium increased to 5.4 milliequivalents per liter on the twenty-seventh day. The protein was 7.1 Gm. per hundred cubic centimeters at the time of discharge. The concentration of sodium was not normal until five months later.

CASE 4.—D. H., a 26 year old Negress, was admitted to the hospital with bullous lesions on the skin and on the buccal mucous membrane of six months' duration. The clinical diagnosis was chronic pemphigus. The result of a Pels-Macht test was 57 per cent. She was treated for sixteen days with 5 cc. of dihydrotachysterol daily. Improvement was apparent on the ninth day. She was discharged on the seventeenth day without cutaneous lesions. A few vesicles persisted on the soft palate. The concentration of calcium in the serum increased during the stay in the hospital from 3.7 to 7.5 milliequivalents per liter. For five months after discharge no dihydrotachysterol was given. After three weeks the skin began to show a few vesicles, and during the next four months they appeared intermittently. Five months after discharge the pemphigus became more severe, and the administration of dihydrotachysterol was resumed. A total of 165 cc. was given within the following thirty-six days. Improvement was evident within two weeks, and at the end of the period there was only a single lesion, on the soft palate. The calcium rose from 5 to 6.3 milliequivalents per liter during the second course. In the succeeding eight months large amounts of viosterol in oil were given. The patient meanwhile remained free from lesions on the skin and mucous membrane.

CASE 5.—R. P., a 48 year old Italian-born woman, was admitted to the hospital with a generalized bullous eruption of three months' duration. One small erosion was noted on the lower gum. In this case there was some doubt of the correct clinical diagnosis, as to whether she had chronic pemphigus or erythema multiforme bullosum. The result of a Pels-Macht test was reported as 49 per cent. During the first three weeks in the hospital without treatment, her condition became steadily worse. Administration of dihydrotachysterol was begun after this control period, and within fifteen days she received a total of 115 cc., 10 cc. daily for the first eight days and 5 cc. daily thereafter. Improvement was noted within a week, and after two weeks no new lesions appeared. She was discharged after the third week, free of lesions. In the interval the concentration of calcium in the serum had increased from 4.5 to 5.5 and that of sodium from 132 to 141 milliequivalents per liter. Three weeks after discharge several blisters appeared on the foot. These subsided without treatment. During the following ten months no other lesions appeared.

CASE 6.—C. M., a 69 year old American man, was admitted to the hospital with a generalized bullous eruption of nine months' duration. On physical examination one lesion was observed on the mucous membrane of the lower lip, in addition to the extensive involvement of the body. During the first week in the hospital, without special treatment, the eruption became worse and the general condition was precarious (fig. 1 *A*). A course of dihydrotachysterol was begun at that time, 10 cc. being given daily for nine days, followed by 5 cc. amounts. In addition, calcium gluconate, 6 Gm. orally, was given daily. On the sixth day after institution of treatment development of new lesions decreased and the old lesions healed. After twenty-six days of treatment, with a total of 180 cc. of dihydrotachysterol, the skin was free of lesions (fig. 1 *B*) and the general condition was reassuring. Administration of the drug was discontinued because of nausea, vomiting and weakness of

the legs. For eighteen days the patient's skin remained clear. After that vesicles and bullae began to reappear, and within a week large areas of his body were involved. A second course of dihydrotachysterol was started, 10 cc. being given daily for six days, followed by 5 cc. daily for seven days. A total of 95 cc. was given in thirteen days. Clinical improvement was evident on the fourth day of

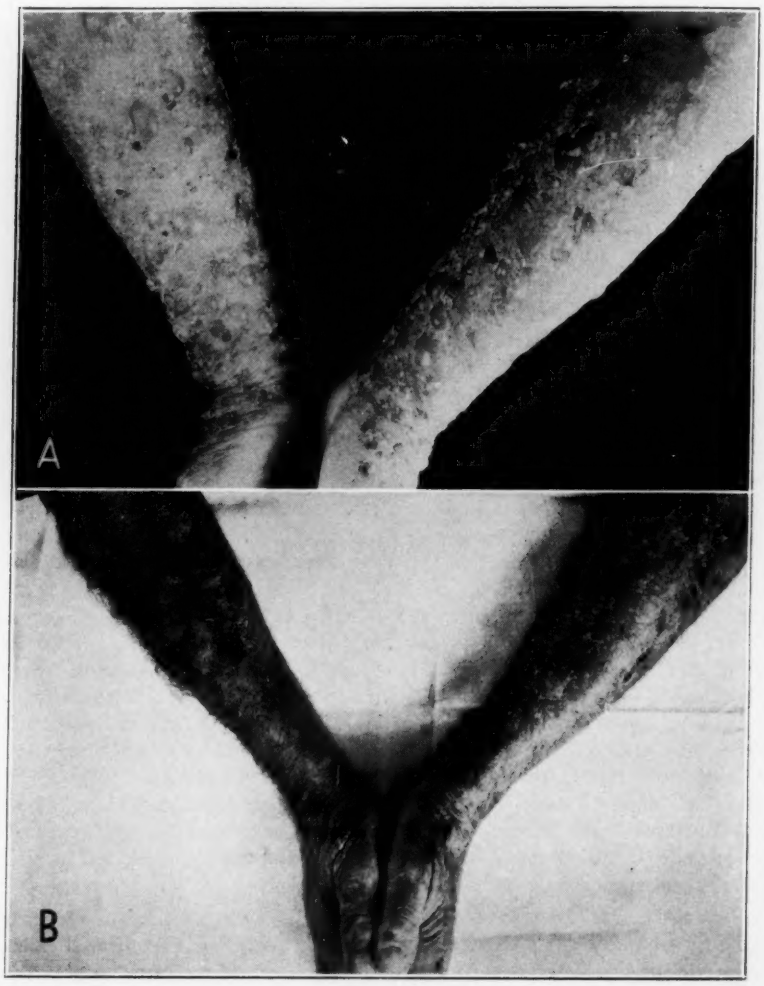

Fig. 1 (case 6).—*A*, appearance of the arms at the beginning of treatment. *B*, appearance of the arms after fourteen days of treatment with dihydrotachysterol.

the second course. Nausea and vomiting, which had appeared at the end of the first course, had disappeared a few days later. On discharge, eleven weeks after admission, the skin showed only a few patches of pruritic, papular erythema. For two months after discharge 5 cc. of dihydrotachysterol was given every second or third day and thereafter 5 cc. every third or fourth day. The patient regained his strength gradually, and three months after discharge, at the age of 70, he

resumed his job as caretaker and chauffeur. At that time the papular erythema had disappeared. Twelve months after discharge the skin was clear except for three small lesions on the chest. Administration of dihydrotachysterol was discontinued after ten months, and 5 cc. of viosterol in oil (50,000 U. S. P. units) daily was substituted.

During the first course of treatment the concentration of calcium in the serum increased from 4.2 to 7.5 milliequivalents per liter and that of protein from 4.9 to 7.9 Gm. per hundred cubic centimeters, while that of phosphate decreased from 4.8 to 2.4 mg. per hundred cubic centimeters. After cessation of treatment the concentration of calcium decreased to 4.9 milliequivalents per liter and that of protein to 6.9 Gm. per hundred cubic centimeters. The effect of the second course of dihydrotachysterol was similar to that of the first. After discharge an attempt was made to maintain the concentration of serum calcium above 5.5 milliequivalents

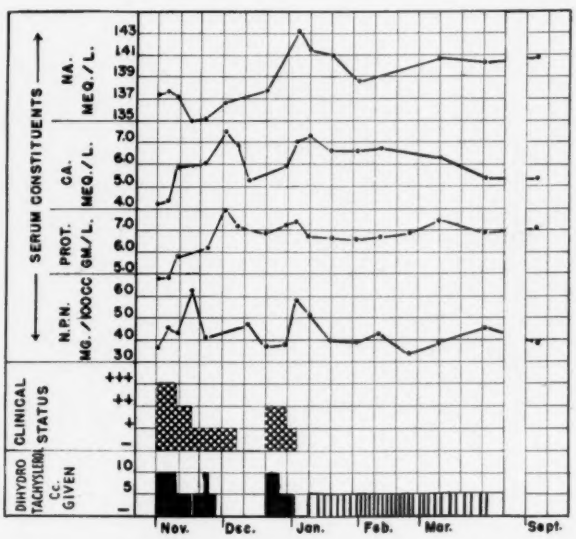

Fig. 2 (case 6).—Concentration of sodium, calcium, protein and nonprotein nitrogen in the serum during treatment with dihydrotachysterol.

per liter and of protein at approximately 7 Gm. per hundred cubic centimeters. On admission the concentration of serum sodium was 137 milliequivalents per liter. This decreased to 135 milliequivalents after three weeks but was restored to normal thereafter. Changes in chloride concentration were similar. The concentration of nonprotein nitrogen was 37 mg. per hundred cubic centimeters of serum on admission; during the two courses of treatment this increased to 63 and 58 mg., respectively, but eventually returned to normal. On the day on which administration of dihydrotachysterol was discontinued finally the nonprotein nitrogen amounted to 39 mg. per hundred cubic centimeters (fig. 2). Mild secondary anemia was present. No changes in concentration of serum potassium were observed. The sedimentation rate remained elevated during the entire period of observation. The volumes of body fluid were determined in the seventh and tenth weeks after admission. The values were similar and above normal. The plasma volumes were approximately 50 cc. per kilogram of body weight and interstitial fluid volumes

approximately 28 per cent of body weight. The urine was examined regularly for albumin and casts. Negative results were reported at each examination.

CASE 7.—B. B., a 45 year old Swedish man, was admitted to the hospital complaining of blisters and scaling of the skin for three months. The skin of the entire body showed erythema, erythematous wheals, coarse exfoliation, flaccid vesicles or denuded areas (fig. 3*A*). The Nikolsky sign was present. A diagnosis of pemphigus foliaceus was made. Treatment with dihydrotachysterol was begun at once, with 10 cc. daily for seven days, followed by 5 cc. daily for fourteen days. After the fourth hospital week 5 cc. was given on two out of every three days. In the thirty-four days of hospitalization 190 cc. of the drug was given. Improvement was noted first on the ninth day of treatment. On discharge, small areas of erythema, patches of parakeratotic scales and a positive Nikolsky sign remained.

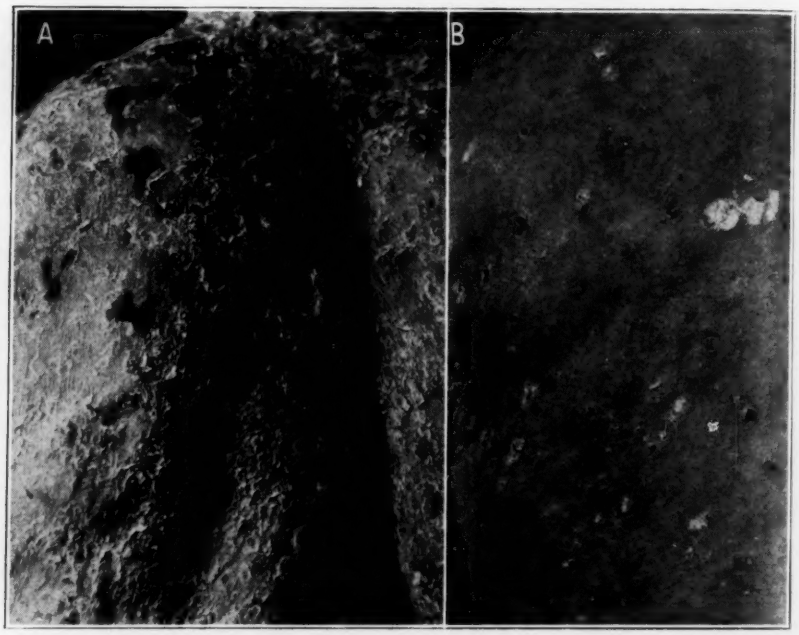

Fig. 3 (case 7).—*A*, appearance of the back at beginning of treatment. *B*, appearance of the back after eight months of treatment with dihydrotachysterol.

Administration of dihydrotachysterol was continued after discharge. During the first month 5 cc. was given on two of each three days, during the second month 5 cc. every other day and during the third and fourth months 5 cc. two days each week. At that time, nearly six months after beginning of treatment (fig. 3*B*), the skin was essentially normal except for mild erythema and scaling in localized areas. The Nikolsky sign was not present. Viosterol in oil, 7 to 14 cc. daily, was substituted for dihydrotachysterol thereafter.

The concentration of serum calcium, as shown in the table, increased from 4.6 to 7 milliequivalents per liter during the treatment; after the initial observation it was not observed below 5.3 milliequivalents. Serum protein had a normal value on admission but during treatment increased more than 2 Gm., to a maxi-

mum of 8.8 Gm., per hundred cubic centimeters. The concentration of serum sodium was slightly below normal on admission and fluctuated in the low range during the period of study. The concentration of serum chloride remained below normal after admission. That of nonprotein nitrogen increased with ingestion of large amounts of dihydrotachysterol. The changes in concentration, however, were reversible. The sedimentation rate was elevated throughout the period of study. The volumes of body fluids were determined on admission and nine months later, when the patient was practically free of lesions. The values were similar and above normal. The plasma volumes were approximately 60 cc. per kilogram of body weight, and interstitial fluid volumes were approximately 31 per cent of body weight.

Experimental Observation on the Blood (Case 7)

	Serum								Whole Blood		Treatment with Dihydrotachysterol			
Date	Total Fixed Base, mEq. per Liter	Sodium, mEq. per Liter	Potassium, mEq. per Liter	Calcium, mEq. per Liter	Chloride, mEq. per Liter	Protein, Gm. per 100 Cc.	Phosphate, Mg. per 100 Cc.	Nonprotein Nitrogen, Gm. per 100 Cc.	Cell Volume, per Cent	Sedimentation Rate, Mm. per Minute	Dates	Total, Cc.	Days After Beginning Treatemnt	Clinical Status*
2/28	150.0	136.2	4.5	4.6	101.5	6.7	3.1	32	46	1.2	.....	..	..	+++
3/ 8	153.0	.....	...	5.8	.....	6.4	3.9	30	..	...	3/ 3-3/ 8	60	6	.....
3/13	.....	.....	...	7.0	.....	6.4	...	47	..	...	3/ 9-3/13	30	11	++
3/17	.....	139.5	...	6.8	94.3	7.1	...	45	45	1.2	3/14-3/17	20	15	++
3/24	.....	138.9	5.2	...	....	6.7	4.1	45	44	1.9	3/18-3/24	35	22	++
3/31	.....	.....	...	7.1	....	7.0	4.4	55	41	1.4	3/25-3/31	20	29	++
4/ 7	149.8	137.8	5.1	6.7	95.4	7.1	3.9	50	39	1.6	4/ 1-4/ 7	25	36	+
4/14	.....	.....	...	5.5	....	6.8	2.5	36	35	1.3	4/ 8-4/14	20	43	+
4/21	.....	.....	...	5.6	....	6.9	2.5	36	35	1.3	4/15-4/21	20	50	+
4/28	.....	.....	...	5.3	....	7.3	...	..	34	...	4/22-4/28	20	57	+
5/ 5	.....	140.7	...	7.9	....	7.9	...	..	34	1.5	4/29-5/ 5	20	64	+
5/12	.....	.....	...	6.8	....	8.2	...	45	35	1.6	5/ 6-5/12	20	71	+
5/19	148.7	137.5	4.4	6.9	97.5	8.8	4.7	32	36	1.8	5/13-5/19	15	78	+
6/ 2	.....	.....	...	7.0	....	8.0	...	48	33	1.7	5/20-6/ 2	35	92	+
6/30	151.7	.....	...	7.5	....	7.3	...	44	..	...	6/ 3-6/30	65	120	+
7/14	.....	.....	...	5.9	....	7.2	...	37	..	...	7/ 1-7/14	20	134	+
8/17	.....	137.9	...	6.1	....	7.0	...	34	32	1.4	7/15-8/17	50	168	+
8/31	148.9	138.3	4.6	6.9	....	7.4	2.1	38	36	1.8	8/18-8/30	20	181	+
	Grand total.....											495 cc.		

* +++ indicates severe involvement; ++, moderate involvement, and +, mild involvement.

Case 8.—C. E., a 47 year old Irishman, was admitted to the hospital with a generalized eruption of vesicles and bullae of nine months' duration. The diagnosis was pemphigus vulgaris. Treatment with dihydrotachysterol was begun at once. He received 10 cc. daily for fourteen days and 5 cc. daily for thirteen days. On the thirtieth and thirty-second days he was given 5 cc. daily. A total of 215 cc. was given in the thirty-two days of his stay in the hospital. Improvement was observed first on the eighth day after beginning treatment. During the third week he complained of nausea and vomiting, which persisted in a mild degree for several days. At the time of discharge his skin was free of lesions. One week after discharge new vesicles appeared. Three weeks after discharge they were present on the arms and neck and in the axillas and groins. Administration of dihydrotachysterol was started a second time, 5 cc. being given daily for fourteen days and then twice a week thereafter for one week. On the twelfth day of the second course marked improvement was evident. He was free of lesions on the twenty-first

day. Viosterol in oil was substituted at that time (7 to 14 cc. daily). Under this regimen he has remained free of lesions for more than six months.

The concentration of calcium in the serum increased from 4.8 to 7.1 milliequivalents per liter and thereafter was maintained above the normal range, at approximately 5.5 milliequivalents. The concentration of protein in the serum increased from 6.6 to 7.1 Gm. per hundred cubic centimeters. That of sodium increased from 136 to 142 milliequivalents per liter. The increase in nonprotein nitrogen was directly proportional to the quantity of dihydrotachysterol ingested. The body fluid volumes were determined on admission, one month later and five months later. The values were similar and above normal. The plasma volumes were approximately 62 cc. per kilogram of body weight, and the interstitial fluid volumes were approximately 30 per cent of body weight.

Case 9.—S. R., a 41 year old Jewess, was admitted to the hospital with cutaneous lesions of five months' duration. There was a butterfly-shaped lesion across the face which was erythematous, scaly and oozing and had slightly infiltrated borders. Vesicles, bullae and scaly patches of erythema were scattered over the face and body. There were several lesions in the mouth. The clinical diagnosis was pemphigus erythematodes. A course of dihydrotachysterol was given, consisting of 150 cc. in twenty-four days: 10 cc. daily for eight days, 5 cc. daily for nine days and thereafter 5 and 2 cc., respectively, on alternating days. On the ninth day after beginning of treatment improvement was evident. It continued gradually but definitely during the following seven months. During the first two months after discharge she took 5 cc. every second day. Subsequently, this dose was reduced to 5 cc. every third day. A few small vesicles appeared from time to time on the legs. The butterfly-shaped lesion on the face and the red, scaly patches on her body continued to regress. She had no systemic complaints.

On admission the concentration of calcium in the serum was 4.9 milliequivalents per liter; this increased to 7.5 milliequivalents during treatment. After discharge the value decreased to the average normal range. The concentration of the other constituents of the serum was normal. The body fluid volumes, determined on admission and three weeks later, were in the range for normal values.

Case 10.—A. A., an 86 year old American woman, was admitted to the hospital with a generalized bullous eruption of five months' duration. She was acutely ill and very weak. Her condition was considered to be grave. Since the renal function appeared to be essentially normal, it was decided to give dihydrotachysterol in spite of her age. She received 5 cc. for twelve days and an additional 5 cc. on the fourteenth day. By the tenth day it was evident that the lesions were regressing. She was allowed ambulatory privileges shortly after and was discharged after sixty-two days in the hospital. There were a few scattered vesicles on the body, but otherwise her skin was in a remarkably satisfactory condition. During the following months her skin was free from lesions.

On admission the concentration of calcium in the serum was 4.5 milliequivalents per liter and that of protein was 5.4 Gm. per hundred cubic centimeters. During the treatment the calcium increased to 7.3 milliequivalents per liter. The protein did not exceed 6 Gm. per hundred cubic centimeters until the sixth hospital week. The concentration of nonprotein nitrogen on admission was 27 mg. per hundred cubic centimeters and increased to 68 mg. with treatment. On discharge it had returned to the initial level. During treatment the urine showed some albumin and a few granular casts. On discharge it was normal.

CHEMICAL STUDIES

The changes in concentration of serum constituents in 34 patients with pemphigus were discussed in a previous communication.[6] In those with the acute form of the disease particular emphasis was placed on a decreased concentration of sodium and chloride and an increased concentration of potassium and nonprotein nitrogen in the serum. The restoration of these concentrations followed the administration of adrenal cortex extract and saline solution. In patients with chronic pemphigus the variations in these constituents were less constant, and no attempt was made to affect their concentrations by any special therapy. Other disturbances noted in both acute and chronic pemphigus included a decreased concentration of serum calcium and protein and an increase in volume of body fluids.

In this study of 10 patients with chronic pemphigus, 5 had a sodium concentration in the serum below 137 millequivalents per liter on admission. The protein concentration in the serum in a similar number was below 5.5 Gm. per hundred cubic centimeters, and in none was it above 6.6 Gm. The reduction was mainly in the albumin fraction, which produced a decreased albumin-globulin ratio. The average concentration of calcium in the serum on admission was 4.4 millequivalents per liter. Large amounts of dihydrotachysterol were given to each patient for the purpose of observing the calcium-raising effect. This was achieved according to expectation, but other changes not expected followed the calcium response, i. e., an increase in the concentrations of protein and sodium in the serum. Regression of cutaneous lesions was concomitant.

The precise mode of action of dihydrotachysterol is not known. According to Albright, Bloomberg, Drake and Sulkowitch,[11] it has two independent effects: (*a*) it increases calcium absorption and (*b*) it increases phosphate excretion in the urine. An increased concentration of calcium in the serum is followed by an increased output in the urine. The calcium-raising effect appears to be related quantitatively to the amount of dihydrotachysterol ingested. With the doses recommended in this communication, an elevation of calcium in the serum may be noticed as early as the third day. The elevation is a slowly progressive process and, owing to an accumulative action, may persist for several days after cessation of treatment. Two weeks may be required before the concentration of calcium returns to normal after cessation of treatment. It seems to us unlikely that the elevation of calcium in the serum

11. Albright, F.; Bloomberg, E.; Drake, T. G., and Sulkowitch, W. H.: A Comparison of the Effects of A. T. 10 (Dihydrotachysterol) and Vitamin D on Calcium and Phosphorus Metabolism in Hypoparathyroidism, J. Clin. Investigation **17**:317, 1938.

specifically and the effect on the calcium in the body generally completely explain the action of dihydrotachysterol in pemphigus. Since the ingestion of dihydrotachysterol is followed by an increased concentration of protein and sodium in the serum, it is reasonable to attribute part of the therapeutic effect to those changes.

An elevation in the concentration of protein in the serum following ingestion of this drug, similar to that observed in our patients, has not been reported previously, although Holtz and Kramer [12] discussed an increase in calcium bound to protein. It would be logical to infer from such a statement that an increase in protein had occurred. The increase in concentration of protein never preceded that of calcium; generally, the response was later. After adequate treatment, all except 1 patient had a protein concentration greater than 7 Gm. per hundred cubic centimeters. In 2 patients (cases 6 and 7) who received dihydrotachysterol for a long time, the protein concentrations were 8 and 8.8 Gm., respectively, per hundred cubic centimeters. In spite of the increase in concentration of protein in the serum which was observed during treatment, no diminution in the volume of interstitial fluid occurred. This was a disappointment, because it had been assumed that the low concentration of protein in untreated pemphigus allowed diffusion of fluid from the blood stream and subsequent increase in volume of interstitial fluid and that a simultaneous restoration would be achieved with an increase in the concentration of protein in the serum. In 3 of 4 patients whose volumes of interstitial fluid were determined before and after increase in concentration of protein in the serum no change was noted.

The decreases in the concentration of sodium before treatment were similar to those reported previously for patients with chronic pemphigus. The diminution, usually, was less than that observed in patients with acute pemphigus but is believed to be significant. A return of the sodium to the average range for normal followed treatment with dihydrotachysterol in each patient. A high normal level was reached in 6 instances. This effect also is thought to be a new observation, although Hoff [13] observed an increased alkali reserve following ingestion of the drug. The observation of Hoff was not confirmed by Holtz.[14] It is presumed that the sodium-retaining property of dihydrotachysterol is similar to that of other steróls, such as desoxycorticosterone acetate and progesterone.[15]

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12. Holtz, F., and Kramer, F.: Wirkungsweise, Indikation und Gefahren von A.T. 10, Therap. d. Gegenw. **77**:241, 1936.

13. Hoff, F.: Untersuchungen über die Wirkung des Präparates A.T. 10 bei parathyreopriver Tetanie, Arch. f. exper. Path. u. Pharmakol. **177**:204, 1935.

14. Holtz, F., in Symposium: Die Tetanie (Nebenschilddrüseninsuffizienz) und ihre Behandlung, Med. Klin. **32**:656, 1936.

15. Thorn, G. W., and Engel, L. L.: The Effect of Sex Hormones on the Renal Excretion of Electrolytes, J. Exper. Med. **68**:299, 1938.

CLINICAL RESULTS

Each of the 10 patients with chronic pemphigus was treated with large amounts of dihydrotachysterol. Clinical improvement in 9 was observed within six to fourteen days after beginning treatment. Improvement in patient 3 was delayed until the fourth week. This delayed response was attributed to the small amounts of the drug which were given. Seven of the 10 were completely free of cutaneous lesions within a month, and 1 patient (case 3), after seven weeks. The other 2 patients (cases 7 and 9), with pemphigus foliaceus and pemphigus erythematodes, respectively, were never completely free of lesions during the period of observation, but they were sufficiently well to be able to lead a normal life and experienced a minimum of handicap from the persisting lesions. Two patients (cases 1 and 2) died three and two months, respectively, after their original course of dihydrotachysterol. One died of pemphigus complicated by bronchopneumonia after administration of dihydrotachysterol had been discontinued for six weeks. The other died of a cerebral accident. It is believed that neither death should be attributed to the use of the drug.

It was apparent that while dihydrotachysterol was useful in the treatment of chronic pemphigus, it was effective only during the period of administration and for a few weeks after. There were only 2 patients (cases 3 and 5) who remained free of lesions after administration of the drug had been discontinued. The cutaneous lesions in case 3 were associated with pregnancy. Before delivery a remission coincided with ingestion of dihydrotachysterol; after delivery the patient remained free of lesions without treatment. In case 5 there was the question of a diagnosis of erythema multiforme bullosum or chronic pemphigus. The skin cleared up coincidentally with the ingestion of dihydrotachysterol. In 5 cases (1, 2, 4, 6 and 8) new bullae appeared within two to four weeks after administration of the drug was stopped. A second satisfactory remission followed subsequent treatment. These observations suggest that clinical improvement was associated with and probably caused by the dihydrotachysterol ingested rather than that it was a natural remission.

The amounts of the drug that were used varied considerably, but in most cases approximately 10 cc. was given daily for a week or ten days, followed by smaller amounts daily for a similar period and eventually by maintenance doses of 5 to 15 cc. per week. The amounts of dihydrotachysterol that were given to each patient were determined by several factors. During the original course it was planned to give sufficient to produce nausea, vomiting and weakness, i. e., symptoms of hypercalcemia. The patients were warned of these symptoms, and none of them became alarmed when they developed. Second, it was noted that a significant

increase in the concentration of protein as well as of calcium in the serum was necessary for satisfactory clinical improvement. After the treatment in the earlier cases, when this observation was made, sufficient dihydrotachysterol was administered to increase the concentration in the serum of protein as well as of calcium. The level of serum calcium, however, was taken as the standard. A sufficient amount of dihydrotachysterol was prescribed to raise the level of the calcium to a concentration somewhere between 6 and 6.5 milliequivalents per liter. This treatment was followed by maintenance doses which kept the level at approximately 5.5 milliequivalents per liter.

During the first weeks of treatment with the drug it seems advisable to hospitalize the patients. In so doing, frequent checks on the constituents of the blood are possible and excessive hypercalcemia with its toxic manifestations may be controlled. The treatment with maintenance doses of dihydrotachysterol may be continued outside the hospital, with studies of blood constituents each week.

DANGERS OF TREATMENT WITH DIHYDROTACHYSTEROL

There are three known hazards from the use of large amounts of dihydrotachysterol: decalcification of bone, excessive hypercalcemia and renal insufficiency. Excessive pathologic decalcification of bone may be prevented by the daily ingestion of 6 Gm. of calcium gluconate. Toxic symptoms from hypercalcemia usually appear as the calcium level exceeds 7 milliequivalents per liter. Nausea, headache, drowsiness and weakness are common complaints. If administration of the drug is not discontinued immediately, drowsiness may progress to coma, and death supervenes from circulatory collapse. In very old patients particular precautions should be taken, as even with relatively small doses the transition from drowsiness to coma may be rapid. Therefore it is recommended that patients in the seventh decade of life or older be given small doses, not exceeding 5 cc. per day, and be watched for any symptoms of toxicity.

The large amounts of dihydrotachysterol which are believed necessary in the treatment of chronic pemphigus frequently result in impairment of renal function. The concentration of nonprotein nitrogen in the serum rises; albumin and casts appear in the urine, and the excretion of phenolsulfonphthalein is diminished. These changes are reversible, however, if the renal function is normal originally. If demonstrable renal impairment precedes ingestion of the drug, irreparable damage may be produced and death from uremia may ensue. It is believed that if the concentration of nonprotein nitrogen is above 40 mg. per hundred cubic centimeters on admission the use of dihydrotachysterol is contraindicated. At the beginning of treatment the nonprotein nitro-

gen averaged 29 mg. per hundred cubic centimeters in the 10 patients and increased to an average level of 51 mg. during the ingestion of large amounts of the drug. During the period of maintenance doses it averaged 32 mg. per hundred cubic centimeters. It is assumed, therefore, that the small doses which are used for maintenance cause no demonstrable damage to the kidneys.

Two patients, not included in the series of 10, died shortly after beginning the treatment. The first one, a woman of 80, died from the toxic effects of hypercalcemia. Dihydrotachysterol in doses of 10 cc. had been given daily for seven days, after which she became drowsy and comatose and died on the eleventh day. The concentration of calcium in the serum had risen from 4.4 to 7.4 milliequivalents per liter, a rapid increase for the amount of the drug given. It is possible that her kidneys were unable to excrete all of the mobilized calcium, although the nonprotein nitrogen content on the day of her death was only 43 mg. per hundred cubic centimeters. Meanwhile the lesions of pemphigus had responded. Another patient, a man aged 78, died from renal failure aggravated by the ingestion of dihydrotachysterol. On admission he had a nonprotein nitrogen content of the serum of 44 mg. per hundred cubic centimeters. After eighteen days of treatment the nonprotein nitrogen was 68 mg. per hundred cubic centimeters and the calcium 7 milliequivalents per liter. Administration of the drug was discontinued at that time, but the value of nonprotein nitrogen continued to rise and on the day of death (the thirty-second hospital day), was 145 mg. per hundred cubic centimeters. In retrospect, the first patient should have been given smaller doses of dihydrotachysterol, while the second patient should not have had any. It is believed that the maximum for patients in this age group is 5 cc. per day. This is illustrated by patient A. A. (case 10), an 86 year old woman who received this amount of dihydrotachysterol daily and who recovered from chronic pemphigus without any untoward effect from the drug.

SUMMARY

Chemical and clinical data on 10 patients with chronic pemphigus are presented.

Decreased concentrations of calcium, protein and sodium in the serum were relatively constant findings. An increase in plasma volume and interstitial fluid volume was observed in 3 of 4 patients on whom these determinations were carried out.

Clinical improvement followed treatment with large amounts of dihydrotachysterol. The improvement was noted first within one or two weeks after beginning treatment. Seven of the 10 patients became free of lesions within two to four weeks and another after seven weeks; they remained well as long as maintenance doses were taken. The other

2 patients, 1 with pemphigus foliaceus and another with pemphigus erythematodes, continued to have a few cutaneous lesions. They were, however, able to live normal lives and pursue temperate activities. Two of the 10 patients died after leaving the hospital from causes not related to the ingestion of the drug under investigation. The administration of the medicine to 5 patients was discontinued temporarily, in each of whom a relapse supervened. Readministration of dihydrotachysterol was followed by a satisfactory remission.

The dangers from the use of large amounts of dihydrotachysterol are discussed. Renal damage may occur but is reversible if not severe. Excessive hypercalcemia leads to drowsiness, and if administration of the drug is not discontinued coma and circulatory collapse may follow. It should be given with great circumspection to persons older than 60. Its use is contraindicated in patients with demonstrable renal insufficiency.

The modes of action of dihydrotachysterol are inadequately understood. The calcium-raising effect in the serum is quantitatively large and undoubtedly important. There are two other effects not hitherto appreciated, namely, elevation of the concentration of protein and of sodium in the serum.

NOTE.—A follow-up study in January 1941 gave the following results:

CASE 3.—The patient was living and well without treatment.

CASE 4.—The patient died of puerperal sepsis. There had been no recurrence of the lesions.

CASE 5.—The patient was living and well without treatment.

CASE 6.—The patient died of carcinoma of the prostate. There were no lesions of pemphigus at the time of death.

CASE 7.—A few lesions persisted. Treatment had been continued with viosterol in oil. The patient had returned to his normal routine of living and working.

CASE 8.—The patient was living and well without treatment.

CASE 9.—A few lesions persisted. Treatment with viosterol in oil had been continued. The patient had returned to her normal routine of living.

CASE 10.—The patient died of general debility eight months after discharge from the hospital at the age of 87. There had been no recurrence of lesions.

LEUKODERMA ACQUISITUM CENTRIFUGUM

REPORT OF A CASE IN WHICH THE CENTRAL NEVI WERE DESTROYED AND THE LEUKODERMIC HALOES THEN TREATED WITH ULTRAVIOLET RADIATION IN AN ATTEMPT TO RESTORE THE PIGMENT

HENRY D. NILES, M.D.
NEW YORK

Leukoderma acquisitum centrifugum is a relatively rare condition, but several articles on this subject have appeared since Sutton [1] reported his 2 cases in 1916. The literature and the various theories proposed to explain the mechanism of the production of these lesions were adequately reviewed by Feldman and Lashinsky [2] in 1936, but I was unable to find any report of what effect, if any, on the surrounding leukodermic area would follow destruction of the central nevus. If, as some authors assume, the nevus drains pigment from the surrounding area, theoretically destruction of the nevus might permit the leukodermic area to regain its normal supply of pigment. An opportunity to study this question was afforded me by a patient with typical lesions of leukoderma acquisitum centrifugum who came to the clinic for removal of the pigmented nevi.

REPORT OF CASE

F. S., a white girl aged 13, was first seen in the dermatologic clinic of the New York Hospital on July 26, 1939. She presented eight small to large pinhead-sized, round and oval, slightly raised pigmented nevi surrounded by round and oval areas of depigmentation, varying from the size of a pea to that of a dime. These were scattered over her face, neck (fig. 1), right arm (fig. 2 *a*), abdomen and back and had been present for one year. There were also some small pigmented nevi without leukodermic haloes and one round depigmented spot without a central nevus on her chest (fig. 2 *b*), back and right arm. The patient's mother stated that the latter had started as white spots and that the first lesion appeared on the right arm. On the right side of the chin was a roughly round depigmented area, the size of a small pea, with two small pigmented nevi in the center. All of the other leukodermic spots contained only one central pigmented nevus.

From the New York Hospital and from the Department of Medicine (Dermatology), Cornell University Medical College.

1. Sutton, R. L.: An Unusual Variety of Vitiligo (Leukoderma Centrifugum Acquisitum), J. Cutan. Dis. **34**:797 (Nov.) 1916.

2. Feldman, S., and Lashinsky, I. M.: Halo Nevus: Leukoderma Centrifugum Acquisitum (Sutton); Leukopigmentary Nevus, Arch. Dermat. & Syph. **34**:590 (Oct.) 1936.

On July 31 the two nevi on the right side of her chin and the one on the right side of her neck were destroyed with light electrodesiccation. When she was next seen, on October 9, these nevi had completely disappeared, leaving only faint

Fig. 1.—Lesions of leukoderma acquisitum centrifugum and of pigmented nevi without haloes.

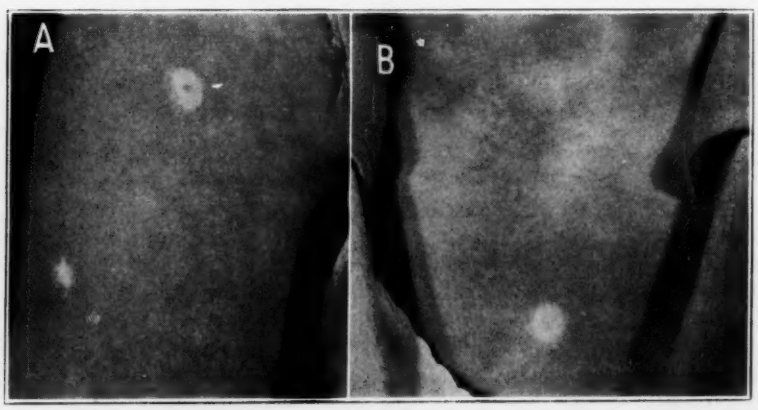

Fig. 2.—*A*, typical lesion of leukoderma acquisitum centrifugum on the arm and, below this, a white spot without a central pigmented nevus. *B*, depigmented spot without a central pigmented nevus.

scarring, but the surrounding white haloes had changed very little in appearance. At this time two nevi without haloes on her left cheek and one with a halo on the left side of her neck and on her right arm were desiccated. On November 22

two other nevi without haloes were desiccated. At this time the haloes around the nevi which were treated in July were definitely fainter and were still fainter when next seen, on December 4.

The patient was not seen again until March 25, 1940. All of the leukodermic haloes were still present around the scars at the sites of the previous nevi over five months after their destruction. Although they were much fainter, this may have been because the surrounding normal skin had lost its summer pigmentation.

On May 20 an erythema dose of ultraviolet radiation was applied to the white spots on the patient's face, neck, chest and back. A few hours later these areas became red, and the erythema persisted for two or three days, but after it disappeared the spots were as white as before the treatment.

On May 27 a pigmented nevus the size of a small pinhead, with the largest white halo the size of a dime, on the abdomen and four smaller pigmented nevi with haloes on the right side of the back were destroyed with electrodesiccation. After this operation all the white spots received another erythema dose of ultraviolet radiation. This again caused the spots to become red, but one week later there was no sign of reaction. The white spots on the face seemed slightly fainter, although the others were unchanged. At this time she received her third ultraviolet irradiation. The patient was last seen on July 15. Although some of the white spots might have become a little fainter, according to the patient and her sister as well as my own observations, none of them had completely disappeared.

COMMENT

The presence of three white spots which never had central pigmented nevi and the persistence of the leukodermic haloes after destruction of the central nevi appear to confirm the conception of Weber [3] and Feldman and Lashinsky that the leukodermic halo is also a nevus and is not merely due to withdrawal of pigment from the skin surrounding the pigmented nevus. The fact that so many of the patients with this condition are children is in favor of Weber's suggestion that the achromic spots are congenital nevi, namely, developmental defects of pigment formation, the opposite of pigmented nevi. If this is true, and judging from the failure of the therapy used in this patient, the only adequate treatment of the white spots would be surgical excision. As patients request treatment of these lesions only because of their cosmetic defect, the scars following surgical treatment would be little, if any, improvement.

I have been unable to find any report of a child with these lesions who was observed up to adult age, but the relative frequency of the occurrence of the lesions in children compared with that in adults suggests that they may often disappear spontaneously. For this reason any radical treatment which might give a poor cosmetic result should not be attempted. None of the articles on this subject makes any mention of treatment. Although this anomaly is rare, the bizarre appearance

3. Weber, F. P.: A Law Regarding the Distribution of Depigmented Patches of Vitiligo, When They Are Superadded to Mole-Like Nevi, Brit. J. Child. Dis. **21**:202 (July-Sept.) 1924.

of these lesions is a source of embarrassment to the occasional patient. The best advice that can be offered at present is to protect these spots from exposure to sunlight so that the contrast with the pigmented surrounding skin can be avoided.

SUMMARY

An attempt was made to restore pigmentation in the leukodermic haloes of several lesions of leukoderma acquisitum centrifugum by destruction of the central pigmented nevi, followed by ultraviolet irradiation of the white spots. The failure of this procedure suggests that the halo is also a nevus, which can be removed successfully only by surgical excision. As this treatment would cause little cosmetic benefit and as some of these lesions may disappear spontaneously, the best course at present is simply to cover the spots with some mild protective and disguising lotion until some better form of therapy is devised.

114 East Fifty-Fourth Street.

LOCALIZED SCLERODERMA WITH BULLAE

H. J. TEMPLETON, M.D.
OAKLAND, CALIF.

The occurrence of bullae with scleroderma is sufficiently rare to justify reporting a case of this kind.

REPORT OF A CASE

Mrs. F. W., an American aged 23, was referred to me during the eighth month of pregnancy by Dr. Dorothy Allen because of coin-sized lesions on her back, chest and abdomen. The patient stated that the lesions began to appear five years previously and had gradually assumed their present form.

When the patient was first seen the lesions on the trunk were apparently in different stages of evolution. Three on her chest, which were said to be the oldest, represented the end stage of some atrophic process, as the skin was depigmented and definitely thinned. On the right scapula there was a lesion about 3 cm. in diameter which was atrophic, depigmented and slightly scaly and showed some telangiectases. On the lower part of the abdomen there was an area measuring 5 by 8 cm. which was rather typical of the edematous stage of scleroderma, being indurated and ivory colored with a lilac border. At this time no bullae were present.

The patient was questioned at length as to whether she had applied any topical remedies which might have produced the blister. She stated that she had not used any local applications and also that she had not ingested any drugs. A specimen was obtained for biopsy, and the patient was referred back to Dr. Allen for a complete medical study; nothing of importance was revealed. Her basal metabolic rate was — 5 per cent.

Two months later a pronounced change had taken place in some of the lesions. Different stages of a bullous reaction could be seen (fig. 1). The most typical bulla occupied the center of the indurated, ivory-colored sclerodermatous lesion on the abdomen. The walls of the bulla were thick, and the material in it was somewhat gelatinous and semiorganized. This bulla differed greatly from the thin-walled, easily ruptured bulla of impetigo or pemphigus. On another lesion an old bulla was drying into a scaly crust. Some of the thinned atrophic lesions aforementioned remained unaltered.

I have observed this patient at intervals for five years. Some of the atrophic areas have remained unaltered. A few new sclerodermatous lesions have appeared at times. These lesions have in time become atrophic. Bullae have become superimposed on some of them, and when they have done so the bullae have persisted for many weeks, slowly turning into scaly crusts and finally falling off.

Histologic Picture.—The epidermis was thinned, and there was marked diminution, and in many areas absence, of the interpapillary prolongations of the rete.

The stratum corneum showed important changes, which consisted of splitting and in certain areas fairly pronounced subcorneal bleb formation. These seemed

so regular and so definitely loculated as to preclude the possibility of their being artefacts. There was no parakeratosis.

The granular layer showed no changes of note. There was no granulosis.

The stratum squamosum was noticeably thinned. A slight amount of cellular edema was noted in the deeper layers of cells near and in the actual basal layer. But when the decided edematous changes in the stratum corneum and pars papillaris were considered, the changes in the stratum squamosum were surprisingly slight.

In the corium two striking changes were evident: edema and lymphatic dilatation in the pars papillaris and definite sclerodermatous thickening of the collagen in the subpapillary and reticular layers. The edema of the papillary layer was apparently a cellular one, as the collagen fibers were swollen and had lost their

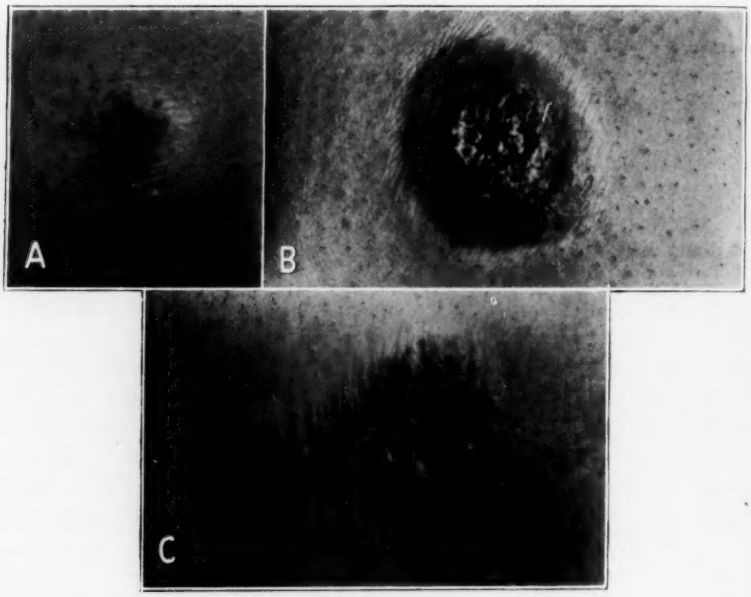

Fig. 1.—Lesion of localized scleroderma showing (*A*) small crust of a bulla undergoing involution in the center and (*B*) and (*C*) old crusted bullae.

affinity for the acid stain. In some areas they were a pale, almost homogeneous mass. All degrees of dilatation of the lymphatics, from slightly dilated lymph vessels to huge spaces, were present in the papillary and subpapillary layers. In some areas the pronounced edema of the papillary layer and the decided dilatation of the lymph vessels combined to form huge lacunar spaces, which were apparently the blebs that were seen clinically.

The reticular area was considerably thickened and was occupied by bundles of collagen which showed a moderate degree of swelling, such as is seen in ordinary scleroderma.

There was no noteworthy invasion of the corium by lymphocytes, nor was there any decided perivascular infiltrate.

The vascular changes consisted mainly of the pronounced dilatation of the lymphatics in the upper layers of the corium.

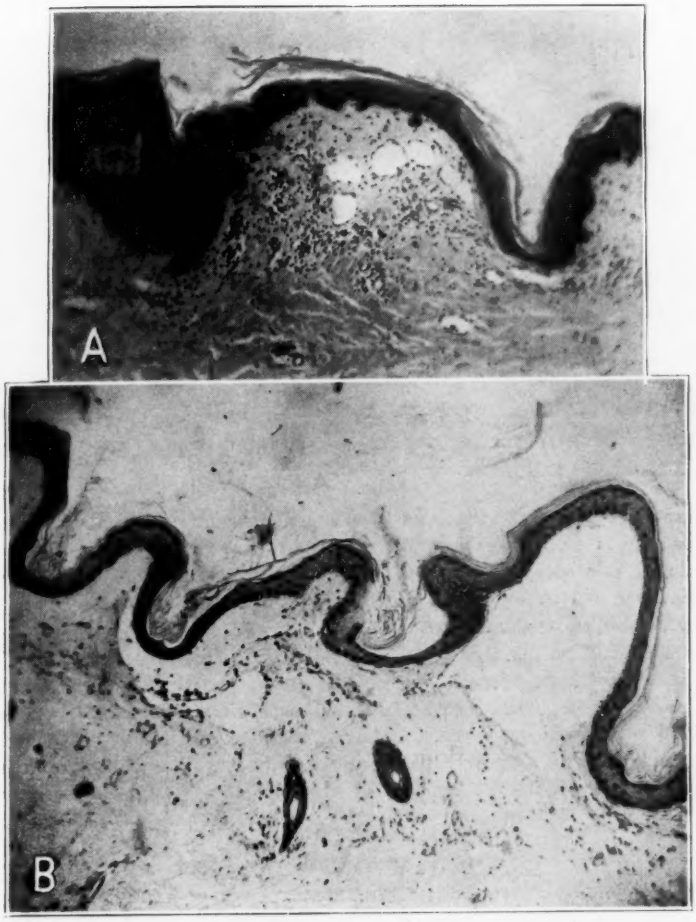

Fig. 2.—Formation of bullae showing (*A*) and (*B*) advanced stage.

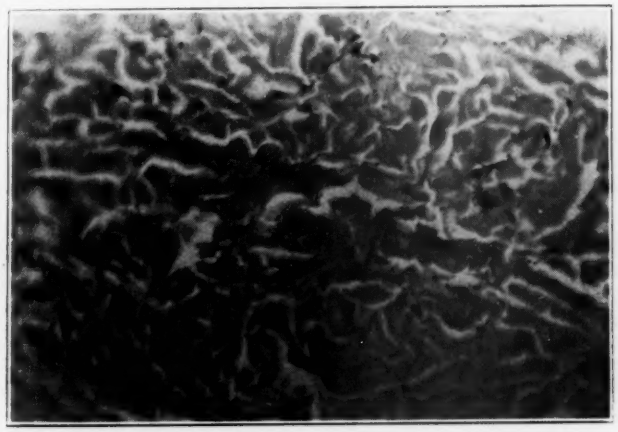

Fig. 3.—Thickening of collagen fibers deep in the cutis.

REPORT OF THE LITERATURE

Jadassohn [1] cited Luithlen [2] as mentioning (from the older literature) several cases of circumscribed scleroderma which showed ulceration and also added that boils can develop from blebs that arise, although rarely, from circumscribed areas of scleroderma. Freund observed a case of typical scleroderma en plaque with clearly defined lilac rings which showed a bleblike lifting of the epidermis in the middle of the sclerodermatous area. Pautrier, citing a case remarkable for the number of affected areas scattered over the entire body, could also establish a formation of blebs followed by ulceration; he expressed the opinion that they were trophic disturbances and attributable to vascular changes, such as arteritis or phlebosclerosis. Dubreuilh [3] stated: "Bullous eruptions have been observed on the fingers." O'Leary [4] described the following case:

> I have under my care at present a woman with somewhat generalized scleroderma which is in reality generalized morphea in the sense that she has a multitude of sclerodermatous plaques, particularly over the abdomen, in which bullae develop and a few plaques on the legs. The bullous lesions are more numerous, however, on the abdomen.
>
> I do not recall having seen a condition like this before, and I have considered it as a more or less traumatic condition with a secondary impetiginous element, because several times when I put her in the hospital and trauma to the area was avoided the bullae did not develop. The impetiginous element is not the primary one, I believe, but is a secondary manifestation of the trauma to the sclerodermatous plaque. I have not observed any case in which bullae appeared on plaques which were not subjected to trauma of some sort.

Sellei [5] stated that he had never seen bullae in association with true scleroderma and suggested that the occurrence of bullae should cause one to consider the possibility of the condition's being dermatomyositis.

COMMENT

This patient was presented twice before the San Francisco Dermatological Society, and on each occasion the majority of the members agreed with the diagnosis of scleroderma. Dr. Howard Morrow saw her in consultation on one occasion and agreed with this diagnosis.

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1. Jadassohn, J.: Handbuch der Haut- und Geschlechtskrankheiten, Berlin, Julius Springer, 1931, vol. 8, pt. 2, pp. 728-729.
2. Luithlen: Sclerodermie, in Mraček, F.: Handbuch der Hautkrankheiten, Vienna, A. Hölder, 1902-1909, vol. 3, p. 128.
3. Dubreuilh, W., in Darier, J.: Précis de dermatologie, ed. 4, Paris, Masson & Cie, 1928, p. 370.
4. O'Leary, P. A.: Personal communication to the author.
5. Sellei, J.: Personal communication to the author.

It has been difficult to account for the formation of bullae on some of the areas. Different consultants considered the possibility that the bullous element was self induced. Against this idea stands the presence of one typical bulla on the patient's scapular region, difficult of access to her fingers. It is conceivable that the ingestion of some drug might cause bullae to become superimposed on preexisting areas of scleroderma. Repeated questioning elicited no history of any drug ingestion.

Driven, then, to theorizing, I should like to suggest that the presence of bullae in sclerodermatous plaques might well be caused by lymph stasis, which could be produced by the dense thickened collagen bundles which are so characteristic of this disease. This would explain the phenomenon as a mechanical blockage, a lymph stasis rather than a trophic disturbance.

Dr. Paul Michael gave his assistance in the histologic study.

COLD ALLERGY AND COLD PATHERGY

ERICH URBACH, M.D.

MAX F. HERRMAN, M.D.

AND

PHILIP M. GOTTLIEB, M.D.

PHILADELPHIA

In cases of hypersensitiveness to cold the condition is not invariably allergic, i. e., based on an antigen-antibody reaction.

Since Duke [1] first called attention to physical agents as the cause of such conditions as urticaria in certain cases, extensive literature on the pathogenesis of hypersensitiveness to cold has appeared. Some authors —including Harris, Lewis and Vaughan; Lehner, Rajka and Török; Prieto, and Bernstein—have adduced all the evidence necessary to demonstrate allergy in their cases. On the other hand, many—including Biberstein, W. Jadassohn and Schaaf and Urbach and Fasal—have never succeeded in performing the passive transfer of this hypersensitiveness and so were never able to prove that the conditions in their cases were based on allergy.

On the basis of the entire pertinent literature and of our own findings (50 cases studied by 1 of us [E. U.] during the past fifteen years and previously reported [2] in part), we believe that hypersensitiveness to physical agents can be based on any of the following types of sensitization mechanisms:

1. Primary physical allergy. Physical agents, such as cold, heat, light and pressure, can become operative on the basis of specific antigen-antibody reactions.

2. Secondary physical allergy. Physical agents can cause the production of secondary antigens in the tissues. The organism may become hypersensitive to these autoantigens.

3. Histamine effect. Under given pathologic conditions the tissue's own protein can undergo alteration, and under the influence of physical agents this altered protein produces a histamine-like substance which elicits, for instance, cutaneous manifestations.

From the Dermatologic Department of the Jewish Hospital; service of Dr. Erich Urbach.

1. Duke, W. W.: Allergy, Asthma, Hay Fever, Urticaria and Allied Manifestations of Reaction, ed. 2, London, Henry Kimpton, 1927.

2. Urbach, E., and Fasal, P.: Wien. klin. Wchnschr. **46**:1069 (Sept. 1) 1933.

4. Cold pathergy. Predisposing factors, such as previous infections and other diseases, can bring about a certain degree of instability in the peripheral neurovascular system. Physical agents are thus enabled locally to elicit abnormal neurovascular reactions.

5. Disturbances of the temperature-regulating mechanism. Central disturbances in the temperature-regulating mechanism, due to previous infectious diseases, attacks of fever or other pathologic processes, may be assumed to be responsible for the pathologic reactions in the blood vessels of the skin in certain cases.

We shall cite examples for each of these five possibilities and shall discuss the mechanisms. First, however, we wish briefly to report a case which clearly shows that specific hypersensitiveness to cold need not be

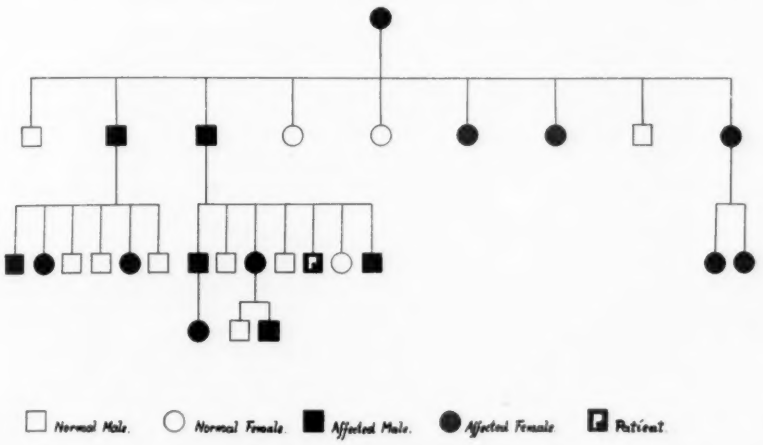

Fig. 1.—Genealogic chart showing 17 cases of hypersensitiveness to cold in four generations. The age of the children increases from left to right.

of an allergic nature. We suggest the term "cold pathergy" to describe this condition. Kile and Rusk [3] have reported the only analogous case in the literature.

REPORT OF A CASE

W. G., 22 years of age, a white, American-born navy yard mechanic, had suffered since birth from manifestations of severe hypersensitiveness induced only by cold air. According to his own and his father's statements, entirely similar symptoms occurred in 17 members of the family in four generations (fig. 1). In all the cases except that of his paternal grandmother, who was the first member of the family to have this condition, the manifestations were present immediately after birth. His grandmother supposedly had measles before her marriage and was exposed to cold during the illness. After her recovery she found that every time she was exposed to cold air she had swelling of the face, arms and legs. In the remaining family history there is no evidence of any form of allergic disease.

3. Kile, R. L., and Rusk, H. A.: Case of Cold Urticaria with Unusual Family History, J. A. M. A. **114**:1067-1068 (March 23) 1940.

The patient himself had no childhood diseases except mumps and no other diseases or allergic symptoms.

From birth the patient had always reacted to prolonged exposure to cold air. If he was exposed for one to two hours, his face, hands, arms, feet and legs, but not his trunk, became swollen and covered with red "blotches," which were about pea sized and confluent or discrete. After further exposure, up to three hours, he began to have a sensation of warmth in his face, and when he then entered a warm room his entire body felt overheated. Oral temperatures up to 101 F. had been recorded but were usually about 100.2 F. If the patient then went to bed, he perspired freely until a normal temperature was reached. The duration of an attack depended on the length of exposure to cold. The shortest attack was at least four to five hours; the longest lasted two full days. The "blotches" which followed the swelling early in an attack, after first becoming worse, disappeared four to five hours after he entered a heated room, but the swelling continued for as long as two days.

Fig. 2.—Urticarial lesions of the face which appeared after the patient spent twenty-five minutes in a cold room (10 F.).

During severe attacks the patient noted throbbing pain and visible swelling in the joints of the hands, knees and feet. The worst attack he recalled was characterized by numbness and complete loss of subjective sensation in the tips of the fingers and toes and extreme "whiteness" of the parts, while at the same time his body felt greatly overheated. The ordinary attack produced by exposure to the usual winter cold did not produce any loss of muscular power, though the patient seemed to have little energy or "pep," but a severe attack produced loss of power in the fingers and hand to some extent. His eyes became "bloodshot" and felt hot during an attack, in proportion to the degree of cold. Sight was never lost. He occasionally experienced headaches on entering a warm room, with a strong desire to sleep.

Cold damp air was worse in its effects than cold dry air. Cold water or ice externally had no effect if the air was warm. Ingestion of cold liquids had no discernible effect on the mucous membrane.

The patient used alcohol moderately, averaging one glass of beer a day, and smoked twenty cigarets a day. He slept about seven hours each night, but during attacks he needed ten hours.

The physical examination showed no abnormalities. The blood pressure was 120 systolic and 70 diastolic, and the pulse rate was 72.

Fig. 3.—Urticarial lesions on the left hand which appeared after the patient spent twenty-five minutes in a cold room (10 F.). The right hand had been kept in a glove.

Fig. 4.—Swelling of the left hand about thirty minutes after the patient left the cold room. The right hand had been kept in a glove.

A complete allergic study, including cutaneous tests, showed no abnormalities.

A commercial preparation of histaminase, in a dose of 60 units daily for six weeks, gave no relief, nor did neo-synephrin hydrochloride, in doses of 60 mg. three times a day for two weeks.

After his only intravenous injection of 10 cc. of a 10 per cent solution of calcium chloride administered slowly, the patient became pale, nearly fainted and had bradycardia, with a pulse rate of 60 per minute. The pallor persisted for ten minutes.

Experimental Investigations.—Neither early nor late urticaria followed the rubbing of the face, extremities and trunk with ice for ten minutes or spraying with ethyl chloride. Similarly, no local or general symptoms could be induced by immersing the whole of both arms in ice water for one-half hour. However, when the patient was stripped to the waist and kept in a refrigerated room (10 F.) for twenty-five minutes, red, urticarial lesions appeared on the face (fig. 2) and on the left hand (fig. 3), while the skin of the trunk remained completely normal. About thirty minutes after he left the cold room, and while he was in a warm room, definite swelling of the left hand appeared (fig. 4), while the right hand, which had been protected by a warm glove, showed neither urticaria nor swelling.

Summary.—A young man evidenced from birth specific hypersensitiveness to cold air but not to the application of other forms of cold. Of the 28 members of his family (four generations), 16 others showed the same type of hypersensitiveness, also beginning at birth. It is particularly noteworthy that only those areas normally exposed to the air (e. g., face, hands and legs) gave reactions. These reactions consisted of local urticarial manifestations and diffuse swelling, as well as certain other symptoms which can be explained only as the result of vascular constriction (piercing pains, followed by numbness and extreme "whiteness"). This vascular constriction was then followed by general vasodilatation (temperature as high as 101 F., feeling of overheating, perspiration and drowsiness). These facts all speak against the existence of an underlying cold allergy, on the basis of an antigen-antibody reaction. On the contrary, they point to specific hypersensitiveness of the peripheral neurovascular system to cold air, a condition which we should like to term "cold pathergy."

USE OF THE TERM "PATHERGY" FOR ALL TYPES OF HYPERSENSITIVENESS AND HYPOSENSITIVENESS

In a forthcoming textbook on allergic diseases [4] there will appear a detailed explanation of the concept that not in every case of hypersensitiveness is the condition to be considered as allergic, i. e., based on antigen-antibody reaction. Moreover, there are a number of phenomena of specific hypersensitiveness which cannot—at least at present—be proved to depend on antigen-antibody mechanisms; for example, there are the light dermatoses, based on porphyrinemia or on isolated stercoporphyria, which can be cured only when the pathologic porphyrin production is controlled (Barber [5] and Urbach [6]), and also cold urticaria, which promptly disappears when a focal infection (Kerl [7]) or a pathologic state of the gastrointestinal tract (Rahier [8]) is removed.

Aside from these specific but not allergic hypersensitivities, there are a vast number of nonspecific hypersensitivities. The latter conditions

4. Urbach, E.: Text-Book of Allergic Diseases, to be published.
5. Barber, H. W.: Practitioner **128**:209-223 (March) 1932.
6. Urbach, E.: Klin. Wchnschr. **17**:304-310 (Feb. 26) 1938.
7. Kerl, W.: Dermat. Wchnschr. **95**:1253-1266 (Aug. 27) 1932.
8. Rahier, C.: Presse méd. **40**:629-631 (April 23) 1932.

are the result—in part at least—of preceding specific allergies. As examples may be mentioned the numerous cases of asthma and eczema in which, although initially specific, the condition begins to react after a while to all manner of chemical, mechanical, atmospheric and even psychic excitants.

For the sake of achieving clarity and coherence in the nomenclature of the various forms of hypersensitiveness and hyposensitiveness, Urbach [4] has suggested the concept of "pathergy" to embrace all the subordinate varieties of abnormal sensitiveness. Together with Roessle,[9] we propose the term "pathergy" to cover any and all pathologic manifestations which are due to altered reactivity, whether there is an antigen-antibody mechanism or not and whether the condition is specific or nonspecific.

According to Urbach,[4] pathergy is to be divided into three main types of hypersensitivity: (1) allergic pathergy, commonly known as allergy, (2) heteroallergic pathergy, subdivided into parallergy and metallergy, and (3) nonallergic pathergy, or, more briefly, pathergy.

PATHOGENESIS OF COLD HYPERSENSITIVENESS

1. *Primary Physical Allergy.*—The existence of true physical allergy, based on antigen-antibody reactions, has been repeatedly and conclusively demonstrated. Nevertheless, we must warn against the assumption that allergy in the strict sense is a frequent cause of these conditions. Working with extensive material, one of us has never yet succeeded in performing a passive transfer with the blood serum (Prausnitz-Küstner) or with the cantharides blister (Urbach-Königstein) methods.

2. *Secondary Physical Allergy.*—In another group of cases the condition may also be considered as allergic, but allergic to substances produced by the action of physical agents on the patient's own skin and muscles. These substances (the so-called secondary antigens or autoantigens) result from some chemical or physicochemical alteration of the tissues; they become foreign to the organism and thus assume the nature of antigens. The brilliant experiments of Karady [10] serve as an excellent example; exposure of the hindlegs of guinea pigs to cold (— 5 C.) or to heat (56 C.) followed three weeks later by reexposure to the same stimulus resulted in anaphylactic shock. Cross experiments between animals treated with cold and heat were negative. These findings, according to Karady, indicate that exposure of the organism to an unusual physical stimulus might lead to chemical-structural changes in the protein of the plasma or cells. Such changes, it would seem, are

9. Roessle, R.: Klin. Wchnschr. **12**:574-581 (April 15) 1933.
10. Karady, S.: J. Immunol. **37**:457-461 (Nov.) 1939.

sufficient to cause denaturization of the protein, which becomes, in effect, foreign to the organism, thus assuming the properties of an antigen (autoantigen).

Plunging into cold water, with consequent sudden cooling of large areas of the body, could cause the production of these autoantigens. This might well explain many of the not uncommon deaths or severe anaphylactic manifestations occurring in bathers.

Furthermore, previous bacterial infections can also make possible the production of such autoantigens. Thus, Burky [11] made the following important demonstration: Rats were prepared with staphylococcus toxin, cultured in a broth made from rat muscle tissue. These rats then reacted anaphylactically to trauma, or, more precisely, to substances released in their own tissues by the trauma.

3. *Histamine Effect.*—The future will have to decide whether the basis of hypersensitiveness in those cases in which the effects of a specific physical agent release a histamine-like substance in the tissues is allergic or pathergic, in short, whether or not there is an antigen-antibody reaction. We are personally inclined to include these conditions among the pathergies. Our assumption finds support in those cases in which the binding of an extremity confines locally the urticarial manifestations produced by the subsequent application of physical agents. The release of the tourniquet is followed by a generalized cutaneous reaction (Horton and Brown [12] and Lehner [13]). Further confirmation is found in the experiments of Lewis and Grant.[14] They collected blood serum from patients with physical allergy after exposing both arms to the influence of the specific physical agent and applying a tourniquet only to one. The serum from the bound arm elicited a decidedly stronger urticarial reaction, both in the patient and in a normal control subject, than did the serum from the other arm. Urbach and Fasal [2] showed that the cantharides blister content from an area of skin made specifically urticarial by pressure was definitely more irritating to the skin than the blister content from a normal area of skin of the same patient.

The presence of a histamine-like substance in these cases seems to be indicated by the findings of Horton, Brown and Roth.[15] They demonstrated that the systemic reactions (e. g., behavior of the blood pressure and pulse rate) following exposure to cold in cases of hypersusceptibility to cold are comparable in every way to the symptoms in

11. Burky, E. L.: J. Allergy **5**:466-475 (July) 1934.

12. Horton, B. T., and Brown, G. E.: Am. J. M. Sc. **178**:191-202 (Aug.) 1929.

13. Lehner, E.: Klin. Wchnschr. **8**:306-309 (Feb. 12) 1929.

14. Lewis, T., and Grant, R. T.: Heart **11**:209-265 (May) 1924.

15. Horton, B. T.; Brown, G. E., and Roth, G. M.: Hypersensitiveness to Cold, with Local and Systemic Manifestations of Histamine-Like Character: Its Amenability to Treatment, J. A. M. A. **107**:1263-1269 (Oct. 17) 1936.

persons who have received injections of histamine hydrochloride. The histamine theory received further support in the therapeutic success achieved by Roth and Horton [16] with histaminase and by Saylor and Wright [17] with injections of histamine.

4. *Cold Pathergy.*—Aside from the evidence in the present case, the following observations lead us to assume that instability of the peripheral neurovascular system may be responsible for the abnormal neurovascular response to local physical agents: (*a*) Both cold and hot baths can cause urticaria (Hopkins, Kesten and Hazel [18]). (*b*) Urticaria can be restricted to certain parts of the body (Musger [19] and Urbach [20]). (*c*) In certain cases manifestations are not elicited by every type of exposure to cold but only by cold water or only by cold air (Biberstein [21] and Klein [22]). (*d*) As reported by Duke,[23] certain persons react to cold only when they have just recently been exposed to heat, or vice versa; i.e., the reaction is elicited by sudden change in temperature and not by the degree of temperature itself. (*e*) Cold hypersensitiveness in certain cases has been cured by the elimination of focal infection (Kerl [7]) and parasitic infestation (Kerl) and by the management of sausage poisoning (Urbach and Greenberg [24]) hypoacidity (Rahier [8]) and hypothyroidism (Créhange [25]). (*f*) As first described by Duke, cold urticaria can be prevented by the local application of heat, and heat urticaria, by application of cold. (*g*) As in the case reported here, the symptoms of vasoconstriction are followed after a while by those of general vasodilatation. (*i*) In this case and in the case reported by Kile and Rusk [3] the hypersensitiveness to cold begins at birth, and about 50 per cent of all relatives in several generations are affected.

In our opinion, all these facts speak for our concept that this group consists of functional disturbances of the vascular innervation or, as it has been termed elsewhere,[2] of "cold-specific vasomotor neuropathy." We now prefer the simpler designation "cold pathergy."

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16. Roth, G. M., and Horton, B. T.: Histaminase in Hypersensitiveness to Cold, J. A. M. A. **110**:686-687 (Feb. 26) 1938.

17. Saylor, L., and Wright, J.: Am. J. M. Sc. **192**:388-395 (Sept.) 1936.

18. Hopkins, J. G.; Kesten, B. M., and Hazel, O. G.: Urticaria Provoked by Heat or by Psychic Stimuli, Arch. Dermat. & Syph. **38**:679-691 (Nov.) 1938.

19. Musger: Zentralbl. f. Haut- u. Geschlechtskr. **45**:149, 1933.

20. Urbach, E.: Zentralbl. f. Haut- u. Geschlechtskr. **45**:149, 1933.

21. Biberstein, H.: Zentralbl. f. Haut- u. Geschlechtskr. **27**:249, 1928.

22. Klein, A. E.: Dermat. Wchnschr. **95**:1741-1746 (Dec. 3) 1932.

23. Duke, W. W.: J. Allergy **3**:257-274 (March) 1932.

24. Urbach, E., and Greenberg, S.: Blood Urticaria, Including Contribution on Metallurgic Genesis of Cold Urticaria, Arch. Dermat. & Syph. **39**:987-991 (June) 1939.

25. Créhange, J. L.: Bull. Soc. franç. de dermat. et syph. (Réunion dermat., Nancy) **39**:440-442 (April) 1932.

5. *Disturbances of the Temperature-Regulating Mechanism.*—It is to be assumed that central disturbances of the temperature-regulating mechanism are the causes of pathologic reactions in the blood vessels of the skin. These derangements are attributable, for instance, to preceding infectious diseases and febrile diseases.

Duke [23] favored this concept, calling special attention to the "reflex-like type," i.e., the condition in which the reaction to cold is not confined to the locally affected site. We do not now see the possibility of establishing experimental proof for this working hypothesis and so cannot express any opinion on this question. Such central disturbances may perhaps be responsible for the general symptoms which are sometimes severe. It is known that merely dipping the hand into cold water occasionally brings on pallor, tachycardia, nausea, spasm of the retinal arteries (authors' case) and fainting spells. It is possible that the cases of death while bathing, described by Grassl and others, may belong in this group.

SUMMARY

Hypersensitiveness to cold can be brought on in a variety of ways: (*a*) allergically, with the physical agent acting as antigen, (*b*) by auto-antigens produced in the tissues under the influence of physical forces, (*c*) by histamine-like substances released in the tissues under the influence of physical irritation, (*d*) frequently and unquestionably, as the expression of an underlying vasomotor neuropathy and (*e*) occasionally, perhaps, by disturbances in the central temperature-regulating mechanism.

Special emphasis is laid on the fact that this variety of possible etiologic factors is of definite importance in the consideration of treatment.

Seventeen cases of urticaria due to cold air occurring in a family of 28 members within four generations are reported.

The necessity for a clear differentiation between allergic and non-allergic hypersensitiveness is emphasized. The concept of "pathergy" is introduced for the purpose of facilitating this differentiation.

CIRCUMSCRIBED MYXEDEMA

REPORT OF TWO CASES

HANS J. SCHWARTZ, M.D.
NEW YORK
AND
RUSSELL F. MADDREN, M.D.
HACKENSACK, N. J.

Myxedema was first described by Gull,[1] sixty-six years ago. He used the expression "cretinoid state" in his account of 5 cases. The term myxedema was coined by Ord a few years later.

Circumscribed myxedema occurs infrequently. In 1883 Kocher [2] reported results of 101 thyroidectomies. He noted that myxedema had a predilection for the lower part of the legs but remarked that in only 2 of his patients was it confined entirely to that region. Handley and Downing [3] recently reported a case of the disease with pretibial nodules and asserted that since Kocher's time only 23 cases of circumscribed myxedema have been recorded in the literature.

REPORT OF CASES

CASE 1.—E. S. G., a 57 year old Chinese laundryman, came to the dermatologic clinic of the New York Hospital in October 1939, complaining of dryness, cracking and itching of both hands.

Past History.—In February 1938 the patient had been admitted to the hospital suffering from toxic nodular goiter, diabetes mellitus and malnutrition. A subtotal thyroidectomy was performed. Three months after admission the man was discharged to the outpatient division for further treatment with insulin.

Physical Examination.—When seen in the dermatologic clinic (twenty months after operation) he was suffering from dermatitis of both hands. In the course of routine examination, large plaques were discovered on the lower anterior aspects of both legs (fig. 1). The lesions had occasioned no discomfort, and he was unable to say how long they had been present. No abnormality of the legs had been noted at the physical examination made before operation. The plaques were

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From the Dermatological Clinic of the New York Hospital and from the Department of Medicine, Cornell University Medical College.

1. Gull, W. W.: On a Cretinoid State Supervening in Adult Life in Women, Tr. Clin. Soc. London **7**:180, 1874.

2. Kocher, T.: Ueber Kropfextirpation und ihre Folgen, Arch. f. klin. Chir. **29**:254, 1883.

3. Handley, F., and Downing, J. G.: Nodular Myxedema Complicating Thyrotoxicosis, Arch. Dermat. & Syph. **40**:374 (Sept.) 1939.

elevated and tawny. That on the left shin was the more extensive of the two. Their surfaces were somewhat irregular. Slight dimpling was present at the follicular orifices, and a resemblance to pigskin was remarked. The plaques appeared edematous but did not pit on pressure. There were no similar lesions elsewhere on the body surface.

Fig. 1 (case 1).—Circumscribed myxedema. Note healing biopsy wound of the left shin.

The patient had been receiving 10 units of insulin daily for several months. His basal metabolic rate and the percentage of blood sugar were within normal limits.

On Nov. 1, 1939, when a biopsy specimen was taken with a punch, mucinous material slowly exuded from the wound.

Subsequent Course.—During the month that he remained under observation, there occurred no observable change in the pretibial plaques. As soon as the condition of his hands improved, he left for California.

Histopathologic Examination.—Dr. N. C. Foot, surgical pathologist to the New York Hospital, examined the tissue removed and confirmed the clinical diagnosis.

Fig. 2 (case 1).—Circumscribed myxedema. Low power magnification showing edema and deposits of mucin in the cutis (hematoxylin and eosin).

Figure 2 well shows the infiltration of the cutis with paramucin, which is the cardinal pathologic change in myxedema. Hyperkeratosis, follicular and sweat pore plugging and perivascular infiltration in the deep part of the cutis would appear to be secondary or consequent phenomena.

CASE 2.—G. R., a 42 year old Hungarian watchmaker, came to the dermatologic clinic of the New York Hospital in April 1940, complaining of itchy swellings on the lower parts of the legs.

Past History.—In June 1939 the patient had been admitted to the hospital suffering from toxic diffuse goiter and hematuria. On July 12 a subtotal thy-

Fig. 3 (case 2).—Circumscribed myxedema.

roidectomy was performed. On the third postoperative day the patient's basal metabolic rate was + 42 per cent. On July 20 he was discharged from the surgical service and referred to the department of urology for further study.

Physical Examination.—When he attended the dermatologic clinic nine months after operation, examination of his legs revealed multiple firm elastic nodules varying in size from that of a bean to that of a pigeon's egg (fig. 3). These nodules were discrete, hemispherical, elevated, movable and of somewhat waxy

and translucent appearance. Some dimpling was present at the follicular orifices, and a resemblance to pigskin was noted. There were no similar lesions elsewhere than on the lower part of the legs.

The patient exhibited decided exophthalmos. His basal metabolic rate was —8 per cent.

Fig. 4 (case 2).—Circumscribed myxedema.

On April 15, when a biopsy specimen was taken with a punch, mucinous material slowly exuded from the wound.

Histopathologic Examination.—Dr. Foot reported that sections showed marked edema of the subcutaneous tissue with disruption of the collagen fibers, atrophy of the epithelium and its adnexae, moderate hyperkeratosis, separation one from another of the small sudoriferous glands and slight perivascular infiltration by lymphocytes (fig. 4).

COMMENT

Unlike Gull's disease, circumscribed myxedema has not been well correlated with hypothyroidism. Morrow [4] referred to a patient with exophthalmic goiter in whom after one year pretibial myxedema of striking symmetry developed. In 7 of O'Leary's [5] cases solid edema developed during acute hyperthyroidism. In the eighth case plaques developed six months before exophthalmic goiter was recognized. The studies of Haines [6] and of Thomas [7] suggest that the problem of causation is not simple. Lord and Morrison [8] stated the belief that multiple endocrine disturbances might be at fault. Richter [9] cited a case of fatal recurrent exophthalmic goiter in which Wolf at autopsy found definite pancreatic lesions. Ingram [10] reported a case of thyrotoxicosis with localized symptoms and discussed the possible predisposing factor of gravitational edema consequent to cardiac failure.

Netherton and Mulvery [11] observed that the small plaques and the nodules of circumscribed myxedema were pruritic, whereas the large plaques were not itchy. Our experience confirmed this finding.

According to Pillsbury and Stokes,[12] the pretibial type of circumscribed myxedema does not yield to the oral administration of thyroid.

SUMMARY

Two cases of circumscribed myxedema are added to the 23 cases already reported. The cause of this condition is not understood, and its specific treatment is as yet unknown.

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4. Morrow, H.: Symmetrical Areas of Solid Edema Occurring in Graves' Disease, Brit. J. Dermat. **11**:286 (July) 1899.

5. O'Leary, P. A.: Localized Solid Edema of the Extremities in Association with Exophthalmic Goiter, Arch. Dermat. & Syph. **21**:57 (Jan.) 1930.

6. Haines, S. F.: Exophthalmic Goiter and Myxedema, Endocrinology **12**:55 (Jan.-Feb.) 1928.

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8. Lord, L. W., and Morrison, S.: Circumscribed Cutaneous Myxedema Associated with Possible Endocrine Disturbances, South. M. J. **26**:231 (March) 1933.

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Clinical Notes

DERMATITIS DUE TO STAIN ON THE WOODEN HANDLE OF A KITCHEN KNIFE

LESTER HOLLANDER, M.D., PITTSBURGH

Mrs. B. Z., a white American business woman aged 56, consulted me on July 11, 1940. She presented a vesiculoerythematous eczema-like eruption which affected the palmar surfaces of the fingers and the thumb of the right hand. It was of nine months' duration. The eruption caused a great deal of inconvenience. It was extremely itchy, and in spite of strenuous treatment, which included roentgen and ultraviolet irradiation and topical applications of all sorts, it persisted with exceptional tenacity.

Questioning brought to light the following information, which was considered of importance from the standpoint of diagnosis:

1. Two years previously the patient had had severe contact dermatitis which was caused by wearing some lacquered wooden ornaments, a bracelet and a brooch. The shortest contact produced a blistery eruption which persisted for from two to three weeks.

2. The present eruption was associated by the patient with a change in her residence from one apartment house to another.

3. In January 1940 the patient went to Florida. Within a few days after she left Pittsburgh the eruption disappeared completely, and she was free from it during her entire stay in Florida. A few days after her return to Pittsburgh she suffered a relapse.

4. Her daily routine was as follows: She arose at 8 a. m., dressed, prepared a simple breakfast for herself and did not look after the cleaning up of the breakfast dishes or the apartment. She was then driven in her car to a point five miles distant from her place of business, from which point she walked to her place of business. There she acted as a cashier for a half-day. During this time a simple lunch was brought in. She was then driven either to the home of a friend or to the home of her daughter, where she usually dined. She generally returned to her apartment about 11 p. m. and pulled down a Murphy bed in preparation for retiring.

5. She had been instructed to wash her hand with olive oil. This usually intensified the itching, so that she had to arise frequently during the night.

6. Careful questioning regarding any lacquered wooden articles failed to reveal any contact substance. Since there was no definite clue, the patient was instructed to remove from her surroundings those articles which usually cause contact dermatitis: plants, ferns, flowers and all lacquered articles. The use of silver and metal polishes and cleaning wax in her apartment and about those articles which she used was interdicted. She was given patch tests with such articles as the strap of her automobile, gloves, various types of dyes and cosmetics, without

From the Pittsburgh Skin and Cancer Foundation.

anything giving any information as to the nature of the true irritant. She was ordered to wear a thin cotton glove, in the hope that she thus might obtain some relief.

After a few weeks of experimentation, because she was insistent that the eruption coincided with her moving into the present apartment, she was instructed to leave it, and stayed at her daughter's for fourteen days. There occurred no improvement. There remained now but two positive factors gained from her history: (1) the previous dermatitis caused by the lacquered wooden bracelet and brooch and (2) the period of complete relief while she was in Florida.

She was questioned again and again in regard to the handling of articles made of wood. Special emphasis was laid on the question of the use of wooden utensils, such as wooden-handled knives or forks, salad spoons and forks. The answer was always in the negative. Requestioning her in regard to eating habits and places, at last I obtained the following information: Before retiring she would go into her kitchenette and cut an orange in half. This was done with a wooden-handled paring knife. She used the same type of paring knife for the same purpose in the home of her daughter during her fourteen day stay. Patch tests with the scrapings of the wooden handles of the two knives were applied, and the reaction was tremendously positive, indeed, to such an extent that after the patches, which stayed on only six hours, were removed, where the normal skin came in contact with the inflamed areas through the bending of the elbow new areas became involved.

This case emphasizes the following facts:

1. A most important step in the recognition of sensitizing agents is careful and detailed questioning and requestioning of the patient. Daily acts are easily forgotten, and in the questioning they have to be practically extracted from patients.

2. Questions regarding simple things seem irrelevant, and these questions are subconsciously resented by the patient (How could such innocent things cause trouble? How could the physician think any one so unobserving as not to have noticed such a simple cause?).

3. The powers of observation of persons are limited. In this patient's case there were three important factors: (1) the history of previous contact dermatitis with the cause known, (2) the absence of dermatitis away from Pittsburgh and (3) the intensity of the itching at night. I was willing to accept the supposition that the intensity of the itching was caused by the washing in olive oil instead of by the handling of the irritant shortly before retiring.

4. In the search for a sensitizing agent one must establish, if possible, some positive leads and then follow through to the most remote possibility. The physician must familiarize himself with the habits, activities, manners, vocation and avocation of the patient. He must know something of the surroundings not only of the patient's abode but also of the places the patient visits.

5. Cotton gloves afford little protection in the highly sensitized person, and if, as in this case, the irritating substance has to do with food, food consumption or food handling, it is possible that the glove will not be worn by the patient at the time of contact.

6. The use of roentgen rays is to be severely criticized before the cause of the dermatitis is learned.

631 Jenkins Building.

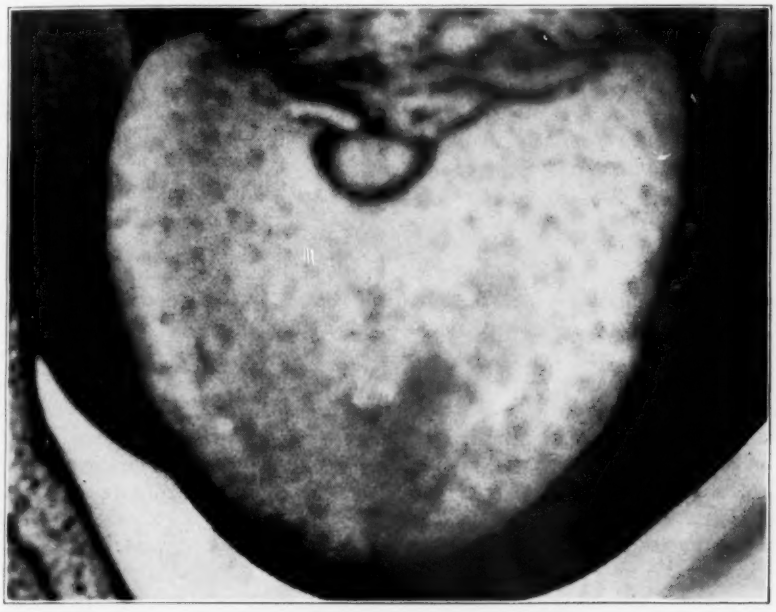
ANNULAR PAPULAR SYPHILID OF THE TONGUE

FRANK C. COMBES, M.D., AND SAMUEL M. BLUEFARB, M.D., NEW YORK

The annular papular syphilid is not an uncommon secondary manifestation in the Negro. The lesions show preference for the face, particularly about the mouth and nose. It is unusual to find them on the buccal mucosa, but instances have been observed in which the lesion was confined to the hard palate. This is the first case in which we have observed lesions on the tongue.

REPORT OF A CASE

L. D., a Negress aged 22, was admitted to Bellevue Hospital complaining of sores about the genitalia and anus of two weeks' duration. Her last sexual



Confluent annular papular syphilid of the tongue.

exposure was three months before admission. Her first complaint was a sore throat two weeks prior to the eruption on the genitalia.

Examination showed moist papules in the anogenital region and a maculopapular rash on the chest, abdomen, back and extremities. An annular papular eruption was noted on the chin, hard palate and center of the dorsum of the tongue. The entire throat was injected, and a mucous patch was present on the right tonsil.

Spirochaeta pallida was demonstrated by dark field examination of material from lesions around the vulva. The Wassermann reaction of the blood was positive. The Frei test and the Ito-Reenstierna test gave negative results.

All lesions responded rapidly to antisyphilitic therapy.

From the Department of Dermatology and Syphilology, New York University College of Medicine, and the Third Medical (N. Y. U.) Division, Bellevue Hospital, service of Dr. Edward R. Maloney.

NONALLERGENIC NATURE OF POISON IVY SMOKE

BEDFORD SHELMIRE, M.D., DALLAS, TEXAS

There is an almost universal belief among both laymen and physicians that dermatitis due to poison ivy may be acquired from contact with the smoke of the burning plant. In order to disprove this fallacious empiricism a person extremely sensitive to poison ivy was exposed to large volumes of smoke from this plant.

REPORT OF A CASE

R. S., a white boy aged 16, living in the house adjoining my own, has been observed during repeated attacks of clinically acquired ivy dermatitis. He is well known among the dermatologists of Dallas, Texas, because of his pronounced sensitivity.

About 25 pounds (11.3 Kg.) of branches and leaves of Rhus toxicodendron radicans was gathered, and the oleoresin from a few leaves of the collected specimens was extracted with ether. Frankly positive cutaneous reactions were elicited on the chest, abdomen, arms, back and thighs of the volunteer when 1 drop of the oleoresin diluted 20,000 times with corn oil was massaged into the tested areas with the finger tip and the tested sites were left uncovered. Serial patch tests repeated during a period of several months proved him to be equally sensitive to the diluted oleoresin of Rhus toxicodendron quercifolia (oak-leaved poison ivy, of the eastern United States) and of Rhus toxicodendron diversiloba (poison ivy or poison oak, of the Pacific coast). He was definitely less sensitive to the oleoresin of Rhus vernix (poison sumac) gathered in eastern Texas.

The 25 pound batch of ivy leaves and branches was allowed to dry for three weeks. Portions of the plants were placed on the cement floor of a room approximately 10 by 12 feet (305 by 366 cm.), and the windows and doors were tightly closed. The ivy was then slowly burned, the fire being repeatedly smothered by the addition of new leaves. The boy was clad only in swimming shorts. The room became so filled with smoke that he and I were compelled to make short excursions to the outside for air. The exposure to the smoke was almost continuous for about thirty minutes, when the entire 25 pounds of material had been burned. On final exhaustion of the flame, the ashes and charred ivy particles were thrown against the boy's naked back, chest, arms and thighs. Several hours later the characteristic odor of ivy smoke was readily detectable on the subject's skin. Bathing was not permitted. Dermatitis did not follow this massive exposure to ivy smoke. One week later the procedure was repeated. On this occasion the volunteer was compelled to hold his face, arms and chest 1 foot (30 cm.) above the smoldering ivy plants, from which dense clouds of ivy smoke arose. Again no evidence of ivy dermatitis developed.

Direct contact with the ivy sap or indirect contact with some sap-contaminated object is necessary for the development of subsequent ivy dermatitis. The oleoresin of ivy is nonvolatile at ordinary temperatures, and the heavy pollen, which is only slightly wind borne, does not contain the dermatitis-producing fraction of the oil. The smoke is nonallergenic at distances of 1 foot or more from the burning plant. Therefore mere excursions into ivy-infested districts will not be followed by subsequent ivy dermatitis if contact with the plant and contaminated objects is avoided.

1719 Pacific Avenue.

HERPES ZOSTER WITH ABERRANT VESICLES

Report of Twenty Cases

SAMUEL M. BLUEFARB, M.D., AND GEORGE E. MORRIS, M.D., NEW YORK

The association of aberrant vesicles with herpes zoster was first noted by Tenneson [1] in 1893. He reported such vesicles in 9 out of 10 cases. Barker [2] stated that many consider this incidence too high. With this in mind, we carefully examined all patients with herpes zoster admitted to the dermatologic service at Bellevue Hospital during the past six months.

Thirty patients with herpes zoster have been observed, of whom 20 (66 per cent) presented aberrant vesicles. The number of aberrant vesicles in each case varied from five to over thirty. They were most commonly seen in elderly patients, on the chest, abdomen and back.

In 12 of the 30 cases the condition was of the gangrenous type, and in 9 (75 per cent) of these there were aberrant vesicles. In only 11 (61 per cent) of the 18 cases in which there were no gangrenous lesions were there aberrant vesicles.

Two of the 30 patients were found to have active, undiagnosed and untreated syphilis of the central nervous system. A third patient was hospitalized for mycosis fungoides. None of these showed varicelliform lesions. Thus, 3 of the 10 patients without aberrant vesicles were found to have an underlying organic disease. It is our opinion, therefore, that when herpes zoster occurs without aberrant vesicles one should always attempt to discover an underlying organic cause.

From the Department of Dermatology and Syphilology, New York University College of Medicine, and the Department of Dermatology and Syphilology, Third Medical (New York University) Division, Bellevue Hospital, service of Dr. Frank C. Combes.

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Obituaries

JOHN TEMPLETON BOWEN, M.D.
1857-1940

Dr. John Templeton Bowen died in Boston on Dec. 3, 1940, in the eighty-fourth year of his life.

He was born in Boston on July 8, 1857, the son of James Bowen and Eliza Matilda (Alline) Bowen. He attended the Boston Latin School and graduated from Harvard University in 1879. His degree of Doctor of Medicine was granted at the Harvard Medical School in 1884, after an intervening service of six months as medical house pupil at the Massachusetts General Hospital in 1883. The summer of 1884 was spent in study in Berlin and in Munich; early in 1885 he continued his graduate medical courses in Vienna, and he remained there until September 1887.

Dr. Bowen was appointed assistant physician to outpatients with diseases of the skin at the Massachusetts General Hospital in May 1889, with Dr. James C. White as his chief. He became physician to outpatients with diseases of the skin in 1895 and held this post until his retirement to the board of consultation in 1914. At the time of his death he was an honorary physician of the hospital.

In 1896 Dr. Bowen was elected instructor in dermatology at the Harvard Medical School and continued at this post until 1902, when, with the retirement of Dr. James C. White, he was appointed assistant professor. In 1907 he became the first Edward Wigglesworth professor of dermatology, resigning in 1911 to become professor emeritus. In 1927 he retired from practice. During these years he had served as consultant in cutaneous diseases at the Children's Hospital and at the Infants' Hospital.

Membership in various medical societies accompanied his active years: the Boston Society of Medical Improvement, the Massachusetts Medical Society, the American Medical Association, the American Dermatological Association in 1889 (its president in 1902), the American Association of Pathologists and Bacteriologists and the Boston Dermatological Club, which later expanded into the New England Dermatological Society.

Through many of these years of service to the hospital, to the medical school and in private practice Dr. Bowen gave a good deal of his time to microscopic study and produced two papers which will always

be associated with his name: "The Epitrichial Layer of the Skin" (1889) and "Precancerous Dermatoses: A Study of Two Cases of Chronic Atypical Epithelial Proliferation"; in consequence of the latter paper European dermatologists have honored him by naming this condition Bowen's disease. From his pen also in these years came numer-

JOHN TEMPLETON BOWEN, M.D.
1857-1940

ous papers as well as contributions to various encyclopedias and "systems."

Dr. Bowen was by nature a student. He loved quiet; he loved his microscope, and he loved to ponder over things—to "mull" over them was a frequent word on his lips. He much preferred this type of life to the public arena of hospital practice and teaching, and it may be said that lecturing was almost torture to him.

This short biography cannot close without due emphasis on Dr. Bowen's great gift for friendship.

While in college he was a member or officer in many clubs, including the Art Club, the Institute of 1770, Delta Kappa Epsilon, the Hasty Pudding Club (president) and the Porcellian Club and an associate member in the glee club. He ended his college career by serving as chief marshal on Class Day, the greatest social honor his classmates could give him.

In later years Dr. Bowen joined the University Club of New York and the Tavern, St. Botolph, Harvard, Country and Somerset clubs in Boston.

As the years passed Dr. Bowen withdrew more and more into himself, finally becoming rather a recluse except to his most intimate men friends; but he still loved to drop in for a quiet chat with an old friend or to take a long walk with others. He loved children, and one who knew him well has said that his letters to her young daughters were a delight, "so full of charm and imagination"—and yet he never married. During his later years he read a great deal and spent many of his summers in Europe, especially in France.

The last years were sad ones. Vertigo developed and became steadily worse, the cause of which puzzled his medical attendants. Added to this trial, as month succeeded month, the afflictions of age developed, and death finally came as a merciful release.

CHARLES J. WHITE, M.D.

Correspondence

CHONDRODERMATITIS NODULARIS CHRONICA HELICIS

To the Editor:—The clinical note by Dr. Kurt Jaenicke which appeared in the ARCHIVES (Chondrodermatitis Nodularis Chronica Helicis, ARCH. DERMAT. & SYPH. **43**:158 [Jan.] 1941) described a small painful grayish red nodule on the anterior surface of the rim of the auricle, attached to the underlying cartilage. It occurred in a nun, and there was said to be "no history of trauma." Electrodesiccation was curative.

In discussing the case of a young woman presented by Dr. Howard Fox before the New York Dermatological Society in 1928 (Chondrodermatitis Nodularis Chronica Helicis, ARCH. DERMAT. & SYPH. **19**:1016-1017 [June] 1929), the late Dr. John Lane said that the nodule was on the anthelix and did not correspond to the condition described by Winkler and Foerster. He had observed similar lesions in nuns, apparently due to pressure from their head dress, and in another woman, due to a tight hat, which also seemed to be the causative factor in Dr. Fox's patient. In 1930 Dr. J. V. Klauder described 3 similar conditions (Klauder, J. V.: Nodule of the Ear Simulating Chondrodermatitis Nodularis Chronica Helicis, ARCH. DERMAT. & SYPH. **22**:833 [Nov.] 1930) in women, 2 of whom were nuns. According to Klauder, these nodules "occur singly, involving one or both ears, and are soft, pink papules; the surface is smooth and flat topped; they are freely movable, not infiltrated and not tender. The lesions are nodular, but in the absence of infiltration they are more properly described as papules. Pain is not a characteristic symptom. They occur on the center, the most prominent part, of the anthelix." He felt that they were due to pressure from tight head dress or telephone ear pieces.

In 1933 I saw a nun with a small pea-sized tender dull red crusted nodule on the helix of the left ear. It was of eighteen months' duration and gradually subsided when pressure from the head band was relieved and zinc oxide ointment applied.

In 1939 a farmer aged 68 consulted me with two tender pinhead-sized pale firm nodules of three years' duration on the helix of the right ear, typical of the condition described by Foerster. Electrodesiccation was followed in two months by the recurrence of tiny tender nodules at the margins of the scars. A second electrodesiccation was curative.

Whether or not such conditions in women should be called chondrodermatitis nodularis chronica helicis, apparently they are usually if not always due to pressure and may or may not be tender.

HOWARD J. PARKHURST, M.D., Toledo, Ohio.

THE GODS DO NOD AT TIMES

To the Editor:—Persons who occasionally try to break into print sometimes suspect the editors of being not only superior but aware of the fact and even, rarely, a bit dictatorial. Seldom is an opportunity offered to "get back" at them. When such a chance appears it should not be neglected.

In the *British Medical Journal* of 1935 (**1**:389 [Feb. 23] 1935), Thomas Moore reported peculiar reactions to gold therapy in 2 cases of arthritis. The second of these was described as follows:

"A man about 30 years of age, with chronic infective arthritis affecting the larger joints and spine, was receiving aurotherapy. He had remarked to me

that particles of gold sometimes came out of his fingers. On one occasion, seven minutes after an intramuscular injection of 0.2 gram of an oily suspension of aurothioglucose, I saw in the sweat on the volar aspects of his fingers shining particles of gold. As this happened after a subsequent injection a very rapid absorption of the salt was suggested. The fact that the sweat glands act as excretory organs for the salt is also very interesting. I have never noticed this in any other case so treated, and have never seen such recorded. It would be interesting to know if others have had a similar experience."

That this report escaped the critical eye of the editor of the *British Medical Journal* was surprising, but the citation of this case as one of several peculiar reactions to gold therapy without further comment by Wile and Courville (Wile, U. J., and Courville, C. J.: Pityriasis-Rosea-Like Dermatitis Following Gold Therapy, ARCH. DERMAT. & SYPH. **42**:1105 [Dec.] 1940) was astonishing. Moore was absolutely correct in believing that he could claim priority in the observation and recording of this phenomenon. The subject should not have been passed over so lightly by writers on the subject of gold therapy. The ability to reduce a gold preparation to the metallic state in one's body is deserving of an extended discussion.

A. W. STILLIANS, M.D., Chicago.

TUBERCULIN SENSITIVITY

To the Editor:—I wish to call your attention to the need for improving reports of reactions to tuberculin tests. The results of such tests are not infrequently reported by the following vague statements: "the tuberculin test was positive (or negative)," "the results of a tuberculin test were positive (or negative)," "the reaction to a tuberculin test was positive (or negative)." Such statements convey little or no information, and it is surprising that they are accepted by the publications of the American Medical Association.

There are many different tuberculins, and there are many different methods of applying tuberculin tests. It is obvious that mention should be made not only of the method employed but of the amount and form of tuberculin used and the time of observation of the reaction.

The most commonly employed tuberculin is old tuberculin (Koch), and the method of choice in this country, especially in cases of cutaneous tuberculosis, is the Mendel-Mantoux (intradermal) test, which permits quantitative estimation of reactions. A proper report, therefore, should read: "Intracutaneous injection of 0.1 cc. of a dilution of old tuberculin (Koch) elicited a positive (or negative) reaction after forty-eight hours."

In the case of a tuberculin patch test, it should be stated whether the reaction was of the usual "delayed" inflammatory type or of the eczematous type.

H. V. MENDELSOHN, M.D., New York.

Abstracts from Current Literature

EDITED BY DR. HERBERT RATTNER

THE FEBRILE TYPE OF ERYTHEMA MULTIFORME. J. S. LEOPOLD, Am. J. Dis. Child. **59**:1298 (June) 1940.

The author describes 2 cases which he believes belong in the category of a febrile type of erythema multiforme. In neither instance were the lesions described except as being typical of erythema multiforme. In 1 instance the lesions involved the entire body, and in the other the face, arms and legs were the sites of the eruption. The striking feature in 1 case was that the eruption appeared at frequent intervals and sometimes lasted but a few hours, all this over a two month period. In the other case the rash disappeared after three days, reappearing at short intervals during a month. During this period the temperature varied from 100 to 105 F. Mild articular symptoms were present in 1 case. In both of these instances the disease occurred in children. NELSON PAUL ANDERSON, Los Angeles.

GENERALIZED SARCOIDOSIS OF BOECK: A CLINICAL REVIEW OF ELEVEN CASES, WITH STUDIES OF THE BLOOD AND THE ETIOLOGIC FACTORS. GEORGE T. HARRELL, Arch. Int. Med. **65**:1003 (May) 1940.

Harrell reviews a series of 11 patients with sarcoidosis observed over a period of years. One patient was an American Indian. The majority were Negroes. Although the etiologic agent remains unknown, it is suggested that the sarcoid reaction may be an exaggerated nonspecific response to a lipid fraction of various organisms.

CRITERIA FOR THE CLASSIFICATION AND DIAGNOSIS OF PERIPHERAL VASCULAR DISEASES. GAMLIEL SALAND, CHARLES KLEIN, HERMAN ZURROW, ABRAHAM GOOTNICK and ABRAHAM KATZ, Arch. Int. Med. **65**:1035 (April) 1940.

The authors review the characteristic signs and symptoms of various peripheral vascular diseases. They point out that proper classification of a patient depends not only on the correct diagnosis but also on the anatomic and physiologic status at the time of examination and a consideration of the functional capacity.

PURPURA HAEMORRHAGICA FOLLOWING NEOARSPHENAMINE AND BISMARSEN THERAPY: FURTHER STUDIES ON SENSITIVITY TO ARSPHENAMINE AND TOLERANCE TO MAPHARSEN. ERNEST H. FALCONER and NORMAN N. EPSTEIN, Arch. Int. Med. **65**:1158 (June) 1940.

Falconer and Epstein continue their study of purpura following arsenical therapy by a review of experimental studies on 6 more patients. Five of the patients in whom purpura followed the use of neoarsphenamine or bismarsen had no apparent reaction after the injection of mapharsen. It is the authors' opinion that these reactions are allergic rather than toxic.

GLOMERULAR NEPHRITIS FOLLOWING INFECTIONS OF THE SKIN. PALMER HOWARD FUTCHER, Arch. Int. Med. **65**:1192 (June) 1940.

Futcher describes 11 patients in whom acute hemorrhagic nephritis followed infected wounds or cutaneous infections. None of these infections of the skin seemed to distinguish itself in severity or in any other way from infections of the same category not followed by nephritis. Only 1 patient did not recover, and his infection had persisted for five months after the onset of nephritis; in none

of the others was the period longer than two months. The author points out that it is difficult to draw pertinent conclusions, since streptococci were also persistently isolated from the pharynx in 7 of these patients. LYNCH, St. Paul.

STUDIES ON THE SITE OF SENSITIVITY IN THE ARTHUS PHENOMENON. A. R. RICH and R. H. FOLLIS JR., Bull. Johns Hopkins Hosp. **66**:107 (Feb.) 1940.

In a series of ingenious experiments involving the cornea the authors were able to show that the Arthus type of hypersensitivity is vascular in nature and that the cells of the tissues at large are not sensitized. The extreme necrosis observed in the Arthus reaction is due primarily to impairment of nutrition resulting from vascular damage.

SKIN, CONJUNCTIVAL AND SCLERAL REACTIONS IN THE COURSE OF THERAPY WITH SULFATHIAZOLE. J. W. HAVILAND and P. H. LONG, Bull. Johns Hopkins Hosp. **66**:313 (May) 1940.

In a group of 78 cases in which sulfathiazole was administered there were 10 instances of dermatitis medicamentosa. In 3 cases the eruption was maculopapular and in 5 instances the cutaneous reaction was "urticarial." These "urticarial" lesions itched moderately and were raised, red, well outlined areas, from 1 to 3 cm. in diameter. They occurred mostly on the extremities. In 2 cases the eruption simulated erythema nodosum, from which it differed in that when resolution took place there was an absence of local discoloration. In 6 instances there occurred injection of the exposed portions of the bulbar conjunctiva and sclera. In 4 of these 6 the condition occurred in conjunction with the drug eruption.

The incubation period varied between four and sixteen days, most commonly appearing between the tenth and twelfth days. Fever was usually present.

In all cases administration of the drug was stopped when the eruption appeared. In 2 instances resumption of the drug reproduced the same type of eruption as before and also on the same sites. NELSON PAUL ANDERSON, Los Angeles.

STUDIES IN ABSORPTION OF UNDIGESTED PROTEIN IN HUMAN BEINGS: VIII. ABSORPTION FROM THE RECTUM AND A COMPARATIVE STUDY OF ABSORPTION FOLLOWING ORAL, DUODENAL, AND RECTAL ADMINISTRATIONS. IRVING GREY and MATTHEW WALZER, J. Allergy **11**:245 (March) 1940.

The absorption of unaltered peanut antigen, which was previously shown to occur after oral and intraduodenal administration, was studied in 31 adults after rectal administration. The authors found that the average absorption rate following rectal administration of the antigen approximated that following its intraduodenal introduction and was more rapid than that following its oral ingestion. In 14 patients with gastric hyperacidity absorption of the peanut antigen from the rectum was slightly retarded, a finding which was also noted following the oral and intraduodenal administration of the antigen in these cases.

MENDELSOHN, New York.

INVESTIGATIONS CONCERNING ACTUAL METHODS EMPLOYED IN THE MANAGEMENT OF COMMON DERMATOSES. J. Invest. Dermat. **3**:143 (April) 1940.

This paper is a symposium on the practical management of acne vulgaris. Six representative dermatologists answered a questionnaire prepared by the editors of the *Journal of Investigative Dermatology* on the methods which they employ in the office management of this disease.

Four stated that they employed roentgen rays routinely in treatment of patients aged 15 to 17 and over, while two stated they used roentgen ray therapy only after the disease failed to respond to a fair trial of local remedies and did not hesitate to employ this method for patients of any age. Two of the physicians thought it necessary to protect the lips when giving roentgen therapy; the others did not.

It was unanimously agreed that there were no untoward after-effects of roentgen therapy when properly handled. Half of the group found diet helpful while half stated that diets were of no value. It was generally agreed that vitamins, vaccines and hormones were entirely without value in treatment. However, one of the men routinely gave thyroid extract and sometimes parathyroid extract. All used various local agents in the form of ointments or lotions, and all but one believed in the surgical removal of comedos and pustules. DAVIS, Nashville, Tenn.

THE GROWTH OF EPITHELIUM IN TEGUMENTARY TISSUES. H. LESLIE-ROBERTS, Brit. J. Dermat. **51**:405 (Oct.); 451 (Nov.) 1939.

The principle of induction, as related to growth and organization, has led to a revolution in biologic thought, with replacement of visible histologic form by chemical conceptions.

According to this view, (1) the ectoderm starts on its course of development incompetent for complete development; (2) the differentiation of the ectoderm into epidermis and nervous material is brought about by induction, and (3) the inductor is a chemical spatial structure present in all parts of the embryo but not capable of inducing so long as it remains within the ectoderm and operating on the ectoderm from the mesoderm, the mesodermal environment being essential to its energizing.

Among the many conclusions reached after extensive research into problems of epithelial growth are the following: No line of demarcation separates normal from malignant growth, for every epidermal organic derivative starts life as a tumor with the potential capacity for becoming malignant. No epithelial cell which has assumed a functional habit of life can dedifferentiate and become the starting point of an epithelial growth the time scale of which deviates from that of the colony to which it belongs. The capacity of initiating epithelial growth resides in the undifferentiated mesenchyme cell endowed with the formative function.

CARO, Chicago.

DIPHTHERITIC ULCERS OF THE SKIN. C. L. PASRICHA and G. JANJA, Indian J. M. Research **27**:643 (Jan.) 1940.

Five patients suffering from ulcers on the legs or feet have been studied. These ulcers occur in Chittagong Hill Tracts and are locally known as "garigha" or "wheeled" sores. A few persons are affected each year during the monsoon rains. Occasionally the disease assumes an epidemic form and many persons are affected. No age or sex is immune. The infection takes place through some injury or scratch, which becomes inflamed and then breaks down to form painful ulcers, which are slow in healing.

Two patients were seen in 1938 and 3 in 1939. From each of the twenty-one ulcers in the 5 patients one organism was regularly and repeatedly isolated. This organism resembled Corynebacterium diphtheriae in its morphologic characteristics and biochemical reactions but was not toxigenic. An extensive study of this bacillus and comparisons with the characteristics of the species in the genus Corynebacterium listed by Bergey (1939) and Topley and Wilson (1936) classify it as a nontoxigenic variant of C. diphtheriae. According to the character of growth on tellurite blood agar and in liquid cultures, its inability to attack starch or glycogen and its hemolytic properties, this organism belongs to the mitis type of C. diphtheriae. Other organisms, such as Streptococcus pyogenes, Staphylococcus aureus and Staphylococcus albus, were isolated from the sores, but with no regularity. All attempts to demonstrate the presence of filtrable virus gave negative results.

The conditions governing the general prevalence of the ulcers and their epidemic rise and fall have not been studied. The contagion is spread by means which are in operation during the rains, but the exact circumstances and their incidental cooperation which give rise to epidemic conditions remain to be studied

and must be studied in the places where these ulcers occur. Wet weather, however, favors the spread of these sores. This contrasts with the dry desert conditions which are favorable to the spread of veldt sores, the causative agent of which has been found by many investigators to be the toxigenic C. diphtheriae.

TISSUE ENZYMES OF THE LIVER AND THYROID IN THE TREATMENT OF ECZEMA IN DOGS. F. MAIGNON, Ann. de dermat. et syph. **10**:737, 1939.

The author had previously shown that it was possible to extract substances from the fresh organs of animals which when administered by ingestion or injection to subjects who had functional insufficiency of those organs brought about the reestablishment of nutritive and functional activity of the organs.

The author also cites the work of one of his pupils, Créquigne, who treated 62 eczematous dogs with enzymes from the liver and thyroid. In 55 animals the eczema completely disappeared and the hair regrew; in 27 there were no relapses in two years, and in 28 there were mild recurrences which responded favorably to the treatment. The 7 cases in which the results were poor were thought to represent eczema of external origin. Maignon states the belief that eczema of alimentary origin in the dog is frequently related to hepatic insufficiency.

ETIOLOGIC PROBLEM OF INDURATIO PENIS PLASTICA. JOSÉ MAY, Ann. de dermat. et syph. **10**:745, 1939.

The author describes a case of induratio penis plastica which in his opinion was due to the virus of lymphogranuloma venereum. In May 1936 multiple ulcers of the coronal sulcus developed in the patient, aged 28. The lesions were at first thought to be syphilitic, but they did not respond to antisyphilitic therapy. In September 1936 the penis became sclerotic and indurated. The lymphatics on the dorsum of the shaft seemed to be involved, which called to mind the disease of Nicolas-Favre. Therapy with Frei antigen was instituted, and regression and healing followed within a year. The serum from the balanopreputial lesions was utilized in preparing an antigen which caused positive reactions in 3 patients who were known to have lymphogranuloma venereum. The author cites a similar case observed by Burzaco. May states the belief that induratio penis plastica may be caused by various infections, including lymphogranuloma venereum.

TUBERCULOUS BACILLEMIA IN LUPUS ERYTHEMATOSUS. L. M. PAUTRIER and SAENZ, Bull. Soc. franç. de dermat. et syph. **46**:1110 (Sept.-Oct.) 1939.

This condition was studied by injecting blood into 41 monkeys. No tuberculosis in the animals resulted.

NATURE OF LUPUS ERYTHEMATOSUS. J. GATÉ and P. CUILLERET, Bull. Soc. franç. de dermat. et syph. **46**:1141 (Sept.-Oct.) 1939.

The authors present the following observations on 24 patients with lupus erythematosus: (1) only 3 were syphilitic, (2) 5 had definite pulmonary tuberculosis, (3) 5 had cutaneous tuberculosis (lupus vulgaris), (4) 2 had papulonecrotic tuberculids and (5) 2 had ocular tuberculosis; (6) in 10 patients attempts at blood cultures were made (Löwenstein's method), and there were five positive microcultures and one visible macroculture.

Of the 24 cases, a tuberculous genesis could be seriously considered in 19 on the basis of clinical, serologic or bacteriologic observations.

ETIOLOGIC FACTORS IN LUPUS ERYTHEMATOSUS. W. LUTZ, Bull. Soc. franç. de dermat. et syph. **46**:1145 (Sept.-Oct.) 1939.

Lutz summarizes his views in the following way: 1. There are a small number of cases of lupus erythematosus in which tuberculosis plays no part and the condition is caused by other toxic substances. 2. In cases of lupus erythematosus

allied to active tuberculosis in which it is difficult to prove the direct association of the two diseases, it seems permissible to say that probably specific substances from the bacillus of Koch do not produce the eruption but that nonspecific substances (such as cellular degeneration products and protein), which develop during the tuberculous infection, are responsible.

LAYMON, Minneapolis.

INVESTIGATION OF THE IRRITATIVE ACTION OF THE LEAVES OF AFRICAN HEMP. W. SCHULZE, Arch. f. Dermat. u. Syph. **181**:63, 1940.

Five hundred and eleven patients were given patch tests with African hemp (Sparmania africana). The leaves were removed after twenty-hour hours. Positive reactions, from 1 plus to 3 plus, were evoked in about 90 per cent of the cases. Severe 4 plus reactions were not elicited.

One hundred and sixty patients were given patch tests with the macerated leaves of African hemp as well as with aqueous and alcohol-ether extracts of the leaves. The macerated leaves produced some positive reactions, but the extracts produced no reactions.

The author concludes that the hairs of the leaves are responsible for the dermatitis.

A CASE OF BENIGN LENTICULAR LYMPHOMA (LYMPHOCYTOMA) OF THE FACE. P. KYRLE, Arch. f. Dermat. u. Syph. **181**:703, 1940.

A woman aged 41 had had extensive cervical lymphadenopathy at the age of 19, which was considered tuberculous and which receded after roentgen therapy. For eight years she had had a series of isolated, sharply circumscribed, rather firm brownish red nodules on the cheeks. The most recent one was removed surgically after having doubled its size in six weeks. Section showed lymphoreticular tissue extending from just beneath the epidermis into the subcutis. Germinal centers were present. The cells were largely lymphocytes, with lymphoblasts in the germinal centers.

The condition had been described as lymphocytoma and had been considered by some as granulomatous, by others as hyperplastic. The author accepts the latter view.

BECKER, Chicago.

CONTRIBUTION TO THE HISTOGENESIS OF GOUTY NODES. S. NIINO, Jap. J. Dermat. & Urol. **46**:1 (July) 1939.

In Japanese literature there are recorded about 20 cases of gouty nodes in the skin. The author reports a typical case of gout in a man aged 25 who for the past seven years had suffered from recurring painful swellings of the joints of the right foot, knees and upper extremities and in whom during the past four years painless nodules had developed on the fingers, toes and ears. These nodules were bean sized and of cartilaginous consistency and were covered with normal skin. Microscopic examination showed that the nodules were located in the cutis and subcutis and consisted of monosodium urate deposited in a homogeneous mass and surrounded by fibrous connective tissue. The vessels were thickened and their lumens narrowed. Because deposits of urate were found in sweat gland coils the author considers the sweat gland as one of the original places of formation of the tophi.

CHANGES IN THE COMPLEMENT FIXATION REACTION IN SYPHILITIC SERUM PRODUCED BY THE ADDITION OF ACIDS, ALKALIES AND ALCOHOL TO THE ANTIGEN SOLUTION. M. HUKUDA, Jap. J. Dermat. & Urol. **46**:25 (Aug.) 1939.

By the addition of a mixture of 0.0025 per cent hydrochloric acid, 0.01 per cent phenol and 6 per cent alcohol to 0.85 per cent solution of sodium chloride in a thirtyfold dilution of cholesterolized alcoholic beef heart extract, the sensitivity of the Wassermann reaction may be moderately increased. Phenol-alcohol and hydrochloric acid–alcohol, as well as alcohol itself, also increase the sensitivity of

the reaction but to a lesser degree, while potassium hydroxide, sodium hydroxide, ammonia water and other alkalis have an opposite effect and may sometimes inhibit the Wassermann reaction. The author attributes the enhancing effect of the acid-alcohol mixture to the activation of the lipoids of the blood serum and, on the other hand, to the increase in the intensity of the function of the extract antigen.

On Experimental Thallium Alopecia. H. Ōba, Jap. J. Dermat. & Urol. **46**:51 (Sept.) 1939.

The author examined histologically the skin and the endocrine glands in rats to which thallium had been administered. These experiments led to the conclusion that thallium alopecia is caused by both direct injury of the skin and dysfunction of the glands of internal secretion.

Influence of Serum of Guinea Pigs Immunized with Rat Sarcoma and Carcinoma on the Growth of Tumor Cells: II. A Study of Tumor Immunity by the Tissue Culture Method. N. Yano, Acta dermat. **33**:55 (June) 1939.

The author immunized guinea pigs with material from Yuge rat sarcoma, Honda rat sarcoma and Flexner-Jobling rat carcinoma and with blood and spleen of normal rats. He added the immune serum of these different guinea pigs to the tissue culture of rat sarcoma and carcinoma and of spleen and mucous membrane of the bladder of the normal rat. He compared the growth of these tissue cultures with those to which the immune serums were not added. It was found that all immune serums exerted a retarding influence on all the cultivated tissues of the rat and that the immune serums did not have specific action. No antigen specificity has been found in a comparison of rat sarcoma with rat carcinoma and also in a comparison of rat tumor tissue and normal rat tissue.

A Case of Pityriasis Versicolor of the Face. S. Ochi, Acta dermat. **34**:4 (Aug.) 1939.

The author reports a case of an 11 year old girl in whom lesions developed on the forehead and cheeks due to Microsporon furfur. He quotes Iseki, who has observed numerous cases of pityriasis versicolor of the face in natives on the island of Palau in the South Seas.

Bloom, New York.

Society Transactions

SAN FRANCISCO AND LOS ANGELES DERMATOLOGICAL SOCIETIES

FRANCES TORREY, M.D., *Chairman*

H. V. ALLINGTON, M.D., *Secretary-Treasurer*

Joint Meeting, San Francisco, Feb. 17, 1940

Balanitis Xerotica Obliterans. Presented by DR. F. G. NOVY JR., Oakland, Calif.

W. H. T., a white missionary aged 54, states that during his childhood he had a tight foreskin which nearly closed over the urethral meatus and could not be retracted. In 1916, at the age of 30, he was circumcised. The operation was difficult because of the firm adhesions. He had to wear a dressing for several months. The wound finally healed, and he had no further trouble until the fall of 1939, when on returning from China, he had difficulty in voiding. This condition lasted for two or three weeks and cleared without any medical care. He has never paid any particular attention to the usual appearance of the glans and does not know how long the changes have been present.

About one month later he again had difficulty in voiding and consulted a urologist, Dr. Miles Griffin, Oakland, Calif., who found a stricture extending about 0.5 cm. from the urethral meatus. A French 16 sound could be passed at that time. Since then the stricture has been dilated to permit the entrance of a French 22 sound. It is Dr. Griffin's opinion that the stricture is not progressing.

The patient presents an eruption which is confined to the glans penis and is made up of irregular, whitish, atrophic areas and areas of telangiectasia, giving the appearance of a roentgen dermatitis. On each side of the frenum are two pinhead-sized keratotic papules. The patient thinks the one on the right side has been present since his operation. The urethral orifice is smaller than normal. In addition, the patient has a few small areas of vitiligo involving the backs of the hands, the chin and the neck.

DISCUSSION

DR. WILLIAM H. GOECKERMAN, Los Angeles: I agree with the diagnosis, although I might apply a different name to the condition; it is evidently precancerosis.

DR. HARRY E. ALDERSON, San Francisco: I have heard the recommendation made at times in cases of this kind that amputation be performed. I should like to ask what Dr. Novy thinks of this procedure. The prognosis is bad. I should also like to ask Dr. Novy how he accounts for the telangiectasia.

DR. F. G. NOVY JR., Oakland, Calif.: I think this case is a good example of the fact that when a new condition is described immediately many cases are reported. This condition is one which sometimes follows circumcision. It may also follow other irritative conditions of the glans. I have not been able to find out anything about the prognosis. This man has had the condition since the age of 30, and he is now 54. There has been little or no change. I hardly think that amputation would be indicated at this time. The stricture is well under control, according to the urologist who is treating him. The telangiectasia is part of the picture, but why I do not know.

Early Syphilis Resistant to Neosalvarsan and Responding to Mapharsen. Presented by DR. EDWARD A. LEVIN, San Francisco.

J. F., a white man aged 33, first reported to the University of California Dermatologic Clinic on Dec. 9, 1939, with an ulcerated lesion on the lower part

of the abdomen and a large ulcer with indurated margins and base in the coronal sulcus. They had been present about one month. There were no apparent secondary lesions. A dark field examination of serum from the ulcer revealed Spirochaeta pallida. The Wassermann reaction of the blood was negative, but the Kahn reaction was strongly positive.

He was given 0.45 Gm. of neoarsphenamine on December 9, 14, 18 and 26 and on Jan. 4, 1940.

On January 9 it was noted that the penile lesion had not healed, although the ulceration on the lower part of the abdomen appeared to be regressing satisfactorily. Further examination revealed a generalized macular syphilid. Dark field examination of serum from the unhealed penile lesion showed numerous spirochetes, and both the Wassermann and the Kahn reaction of the blood were strongly positive.

The patient was then given 0.06 Gm. of mapharsen on January 9 and January 12.

By January 20, when he was given his third dose of 0.06 Gm. of mapharsen, the penile lesion was rapidly healing and the secondary eruption had almost cleared. Since then he has had four treatments consisting of coincidental injections of 0.06 Gm. of mapharsen intravenously and 1 cc. of bismuth subsalicylate in oil intramuscularly.

DISCUSSION

DR. E. K. STRATTON, San Francisco: During the past twenty-five years, S. pallida, in its travels from one human host to another, has obviously been subjected to the effects of sublethal doses of neoarsphenamine. It is possible that this may account for the resistance encountered in certain syphilitic persons who are treated with this drug. The satisfactory response following the use of another arsenical of different formula, such as mapharsen in this case, suggests such a possibility.

DR. N. N. EPSTEIN, San Francisco: It should be pointed out that in this case the patient received what some physicians would consider as somewhat less than the usual dose of neoarsphenamine. He received three injections of 0.45 Gm. at five day intervals and then two injections of 0.45 Gm. at eight or nine day intervals. I do not think one can say there is a true resistance to the drug unless larger doses than this are given. The person from whom this patient contracted the disease had secondary syphilis and responded well to mapharsen. She had not been given neoarsphenamine.

DR. MERLIN T.-R. MAYNARD, San Jose, Calif.: In the Santa Clara Valley the cases of neoarsphenamine-resistant syphilis are increasing. Most of the patients are Mexicans, either from the Los Angeles region or from across the border. It might be that a tropical strain of the spirochete causes the resistance.

DR. EDWARD A. LEVIN, San Francisco: In answer to Dr. Epstein's remarks, this patient weighed only about 130 pounds (59 Kg.). I felt that five injections each of 0.45 Gm. of neoarsphenamine given over a period of twenty-five days could be considered adequate in this case. I should like to ask Dr. Maynard how many cases of neoarsphenamine-resistant syphilis he has encountered in the past year or so.

DR. MERLIN T.-R. MAYNARD, San Jose, Calif.: I have observed 3 cases in the past three years. In 1 the disease was in the primary stage and in the others in the secondary stage. Two of the patients were finally given malarial treatment.

DR. WILLARD M. MEININGER (by invitation), San Francisco: In regard to drug fastness, a paper by Beckh and Barnett on early syphilis (Beckh, W., and Barnett, C. W.: *Arch. Int. Med.* **63**:974 [May] 1939) revealed a higher incidence of relapse in the series of patients receiving heavy metals and a comparatively low weekly dose of neoarsphenamine (0.45 Gm.) simultaneously throughout forty weeks of the course than in a series treated with the usual alternating plan of therapy. It was believed that prolonged administration of rather small doses of an arsenical might explain the inferiority of the combined system of treatment.

DR. THOMAS J. CLARK, Oakland, Calif.: In the old days very severe types of syphilis were seen. In many of the cases the disease went undiagnosed for long periods, and the dermatologists reaped a rich harvest. Therapeutic measures were based on the use of mercury, and there was sodium cacodylate to fall back on. Such substances in the background as Zittmann's decoction (a compound decoction of sarsaparilla) were used in cases of this kind. With more efficient remedies, such as there are now, fewer cases of resistant syphilis will be encountered.

A Case for Diagnosis (Edema of the Penis Due to Syphilis? Lymphogranuloma Venereum?). Presented by Dr. EDWARD A. LEVIN, San Francisco.

R. M., a white seaman aged 38, states that in November 1938, while in French Indo-China, he noted bilateral swelling and pain in the inguinal region. This was about four days after sexual intercourse. About three days after the onset of his

Photograph in a case for diagnosis (edema of the penis due to syphilis? lymphogranuloma venereum?).

symptoms he noted a penile lesion. The ship's physician gave him two intravenous injections, with some relief. He was then hospitalized in Japan for six months. During this time he received intravenous and intramuscular treatments (type unknown). He was discharged free of signs and symptoms and then returned to the United States.

In August 1939 sore throat, a sore and edema of the penis and a cutaneous rash developed. On his first visit to the University of California Dermatologic Clinic, on November 7, Spirochaeta pallida was obtained from the penile lesion. A Wassermann reaction of the blood was strongly positive. At that time, because of prominent edema of the penis, a Frei test was performed, with positive results.

To date the patient has received ten injections of neoarsphenamine, 0.6 Gm. each, and three injections of bismuth subsalicylate. There is still a residual thickening of the prepuce, although about 75 per cent of the edema has cleared.

From the history and the result of the Frei test, the patient undoubtedly had lymphogranuloma venereum. Might it be that the combination of the two diseases accounted for the edema?

Interstitial Keratitis Developing During Antisyphilitic Therapy. Presented by DR. EDWARD A. LEVIN, San Francisco.

D. K., aged 29, was found to have a positive Wassermann reaction of the blood in 1937, when she was three months pregnant. After receiving eight intramuscular injections of a bismuth compound and eight intravenous injections of neoarsphenamine, she gave birth to a healthy baby in December.

The patient came to the University of California Dermatologic Clinic for further treatment in October 1938. Examination showed no signs of congenital syphilis. There was no history of acquired syphilis. The patient's mother was syphilitic.

Treatment, started in October, consisted of alternate courses of neoarsphenamine and a bismuth compound. When the patient was in the middle of her third course of bismuth therapy symptoms of interstitial keratitis appeared. She had received approximately thirty injections of a bismuth compound and sixteen injections of neoarsphenamine without interruption before the onset of ocular symptoms, in November 1939.

At present the patient shows decided improvement after three sessions of pyretotherapy administered with blankets and body bake, with temperatures of 40, 40.5 and 40.5 C. (104, 104.9 and 104.5 F.), respectively, for four hours.

DISCUSSION

DR. N. N. EPSTEIN, San Francisco: When this patient returned to the clinic, there was a question as to whether she should be treated for syphilis because she did not have any clinical signs of the disease.

It has been my experience that interstitial keratitis responds well to nonspecific fever therapy. In my cases I have used mechanically induced fever. This patient's condition was severe three weeks ago, when fever therapy was instituted, and her response has been unusually rapid.

DR. ARTHUR FLETCHER HALL, Santa Monica, Calif.: I think it might be of some interest to mention the case of a woman aged 20 who was treated for interstital keratitis. While this condition was clearing, eighth nerve deafness developed, which showed definite improvement when she was given malarial therapy, and audiometric tests proved that she almost entirely regained normal hearing. Although the interstitial keratitis had been clinically inactive for two years previous to the malarial treatment, her vision improved noticeably along with the deafness.

DR. KENDAL FROST, Los Angeles: I have a patient with interstitial keratitis, a woman of about the same age as this patient, who had several relapses immediately on cessation of treatment. She was given malarial therapy and has remained clear for the past two years. Another patient, whom I have seen with Dr. Russell Anderson, is a Chinese youth, also of about the same age as this patient, who has had iritis. He has had relapses during the administration of both neoarsphenamine and mapharsen. He was recently given arsphenamine, and the ocular condition has remained clear. He is under treatment now, and his subsequent course is questionable. For personal reasons he is unable to be hospitalized for fever therapy. A group of patients with interstitial keratitis in the service at the Los Angeles General Hospital have been treated routinely with malaria, with uniformly good results.

DR. E. K. STRATTON, San Francisco: About two years ago I did some experimental work on rabbits, inoculating emulsion from chancres into their corneas. In 2 of them chancres developed on the eye. The serologic reactions of the blood of these animals remained negative throughout the course of this reaction. Popliteal gland transfers from these animals to the testicles of new rabbits were also negative. Later, after all of the active ocular symptoms had subsided, I inoculated the testicles of these 2 rabbits with the same strain of Spirochaeta pallida as was used in the corneal infections and obtained "takes" (chancre formation). Such

experiments indicate how completely isolated the cornea is from the bodily defense mechanism, and therefore disappointing results obtained with parenteral medication in cases of interstitial keratitis are not surprising.

Scleredema Adultorum. Presented by DR. N. N. EPSTEIN, San Francisco.

G. M., a white boy aged 5 years, was first seen in the University of California Dermatologic Clinic on Jan. 4, 1940. About eight weeks previously he had a sore throat. One week after this hardening of the skin developed, which was first noted on the back of the neck. Examination showed nonpitting firmness of the skin. The condition was most noticeable on the face, neck, scalp and shoulders. The induration became progressively less evident distally. The hands were only slightly affected, and the feet appeared normal. On the back of the neck there were several healing pyogenic lesions.

The results of the remainder of the physical examination were essentially normal except for evidence of healed rickets (changes in the parietal bones, flaring of the costal margins and beading of the ribs).

Examination of the blood showed 82 per cent hemoglobin, 4,400,000 erythrocytes, 7,000 leukocytes and a normal differential count. The plasma cholesterol was 170 mg. per hundred cubic centimeters. The basal metabolic rate was + 9 per cent. The Wassermann and Kahn reactions were negative. The reactions to tuberculin, both human and bovine, were negative with a dilution of 1 : 1,000.

Roentgenograms of the chest were normal. Roentgenograms showed caries of all the teeth.

Microscopic study of sections of a biopsy specimen from the back showed that the epidermis and the upper part of the corium were essentially normal. There were no pathologic changes in the blood vessels. The deeper portion of the corium was greatly thickened, owing to an increase in the number and size of the collagen bundles. There were some irregularly sized spaces between these bundles and about the sweat glands.

DISCUSSION

DR. WILLIAM H. GOECKERMAN, Los Angeles: I agree with the diagnosis. This condition follows various types of infection in children. I have not encountered any cases of this kind lately in private practice, but a few years ago there were a good many, seemingly mostly after the influenza epidemic of 1918 and 1919. Many observers still look on the condition as scleroderma, but scleredema is undoubtedly a definite clinical picture. I found that while the condition in many cases cleared up spontaneously, injections of foreign protein materially helped in others. The response was, on the whole, satisfactory.

DR. ERVIN EPSTEIN, Oakland, Calif.: In a recent survey of the literature I reviewed reports of about 50 cases of scleredema adultorum. In about 10 per cent there was no infection at any time; in 15 per cent the so-called infection came on after the cutaneous lesions appeared; in about 50 per cent it was described as influenza, but the diagnosis was not proved by the establishment of leukopenia or by the presence of an epidemic; in 15 per cent there was an infection of the upper respiratory tract, and in only about 10 per cent was the infection specific, such as measles or erysipelas. I wonder if the so-termed preceding infection might not be simply a prodromal condition, such as is seen in scleroderma or erythema multiforme, and not of etiologic significance.

DR. WILLIAM H. GOECKERMAN, Los Angeles: I do not believe that such a study means much. I am satisfied that while one cannot always get a history of infection, such a history is obtainable in about 80 per cent of cases, if the investigator searches for it carefully.

DR. N. N. EPSTEIN, San Francisco: One does not have the opportunity of seeing many patients with this condition. This case is the first I have had in a number of years. The more I see of this condition, the more it seems to me to be a separate clinical entity. There is true edema deep in the corium which

resolves without vascular changes, such as are seen in scleroderma. There seems to be a definite episode of infection that precedes the condition, if the history is gone into thoroughly.

Ehlers-Danlos Syndrome. Presented by DR. HIRAM E. MILLER, San Francisco.

C. B. J., a white girl aged 5 years, was born with "a congenital hip," which was corrected shortly after birth.

The patient presents (1) overelasticity of the skin, (2) overextensibility of the joints, (3) friability of the skin, (4) pseudotumors of connective tissue and (5) pea-sized, freely movable spherules under the skin. The spherules can be noted on the outer sides of the thighs.

These five complaints are the cardinal points of this syndrome. The shot-like spherules deep in the subcutaneous tissue of the outer part of the thighs are of particular interest.

The patient wears an elastic bandage about both ankles because she is constantly spraining them.

A Case for Diagnosis (Necrobiosis Lipoidica Diabeticorum?). Presented by DR. ROBERT A. STEWART (by invitation), San Francisco.

S. R., a white woman aged 70, was presented before the San Francisco Dermatological Society on Nov. 17, 1939 (ARCH. DERMAT. & SYPH. **41**:1143 [June] 1940).

During this month additional laboratory studies were made. Dextrose tolerance studies showed the following results: fasting blood sugar, 127 mg.; one-half hour, 235 mg.; one hour, 263 mg.; two hours, 328 mg.; three hours, 234 mg., and five hours, 141 mg., per hundred cubic centimeters. The plasma cholesterol amounted to 167 mg. per hundred cubic centimeters. The basal metabolic rate was + 3 per cent.

DISCUSSION

DR. WILLIAM H. GOECKERMAN, Los Angeles: In this case there is not, of course, the definite clinical picture of necrobiosis lipoidica diabeticorum. Nonetheless it is possible that this particular phenomenon may occur in cases in which the background is the same but the classic picture does not appear.

The point I want to make is that one does not need to see the entire classic picture in order to make the diagnosis of necrobiosis lipoidica diabeticorum.

DR. HIRAM E. MILLER, San Francisco: Belote and Welton (ARCH. DERMAT. & SYPH. **40**:887 [Dec.] 1939) reported necrobiosis lipoidica diabeticorum in a patient who did not have diabetes. In the discussion it was argued that the patient might have had diabetes before coming under observation. The answer to this argument was that new lesions had developed while the patient was under observation and without diabetes.

Actinomycosis. Presented by DR. H. J. TEMPLETON, Oakland, Calif.

A. H., a white American girl aged 14, consulted the presenter on Nov. 20, 1939 because of a draining sinus in the skin over the left mandible.

A lower left molar tooth was extracted on June 19. Within two weeks a lump developed over the left mandible. This was opened by her dentist, with the release of some blood and pus. It was lanced, probed, cauterized and scraped on several occasions by her dentist and by her physician.

When seen, the condition was about as it is today, i. e., an indolent granulomatous, discharging swelling, measuring about 1 cm. in diameter.

Roentgenograms of the jaw showed no changes in the bone or teeth. The Kline reaction of the blood was negative. Smears for tubercle bacilli were negative. The tuberculin test gave negative results. A complete blood count was normal. A wet preparation of the pus showed the presence of actinomycotic granules.

The administration of sulfanilamide, 30 grains (1.9 Gm.), daily for one month, produced no improvement. While taking this drug she was given 350 r of filtered roentgen rays on four occasions, without improvement. In the last month she has taken potassium iodide in rapidly ascending doses by mouth. During the last two weeks the dose has been 100 drops (6 cc.) of the saturated solution three times a day. No improvement has been noted.

She is presented for suggestions as to therapy.

DISCUSSION

DR. NELSON PAUL ANDERSON, Los Angeles: I should like to question the diagnosis of actinomycosis in this case. I think there are several arguments against this diagnosis: 1. The patient seems to have a single sinus opening. 2. The demonstration of organisms of actinomycosis is not always evidence of true actinomycosis; one would have to make anaerobic cultures in such a case. 3. I should like to suggest that this lesion is probably of the same nature as a persistent sinus tract, probably due to osteomyelitis following removal of a tooth. There is a peculiar dimpling in the upper part of the lesion in which I think one could demonstrate a fibrous band leading to the periosteum. I suggest that anaerobic cultures be made, that roentgenograms be taken with iodized poppyseed oil and with the insertion of a silver wire into the sinus tract and that roentgenograms be taken also from beneath the jaw to prove or to rule out the presence of an osteomyelitic focus.

DR. MERLIN T.-R. MAYNARD, San Jose, Calif.: I should like to second Dr. Anderson's opinion that the condition might easily be osteomyelitis. I examined the patient and was skeptical of the diagnosis but after seeing the microscopic preparation thought it might be correct. I saw a child with a similar condition. No actinomycosis was found, but a bit of tooth was discovered by means of roentgen rays at the base of the sinus. After that was removed there was quick recovery. I think that in this case roentgenograms should be made of the entire mouth in case there is an osteomyelitic process at the base of another tooth.

DR. C. J. LUNSFORD, Oakland, Calif.: The organisms were demonstrated on many occasions and seen by different pathologists in Oakland, as well as by myself. Every one was satisfied with the diagnosis.

DR. HARRY E. ALDERSON, San Francisco: It is known that sulfanilamide and roentgen therapy were both given in this case. Sulfanilamide will cause solar sensitization. Lately I have heard roentgenologists say that they are afraid to give roentgen ray treatments after the use of sulfanilamide. Does any one know anything about this?

DR. SAMUEL AYRES JR., Los Angeles: I think one should give serious consideration to vaccine therapy in this case. Dr. H. D. Jacobson, Los Angeles, has had very good results with vaccines prepared by the Krueger method.

DR. HENRY SUTHERLAND CAMPBELL, Los Angeles: Proving an actinomycotic infection in man is not an easy task. The culturing of the sulfur granules appears to be as difficult as their classification, which has placed them among the fungi imperfecti. There are many actinomyces, normally saprophytic. Some may under stress become parasitic, but here again differences obtain, for some of them invade but superficially while others produce the deeper sinus formation. It appears that only in cases of the latter are the sulfur granules met with. The granules are believed by some to be fungi; others, of undoubted experience, maintain they are clumps of bacilli. I have failed consistently in my efforts to culture the washed sulfur granules taken from the discharge from the human sinus, using a variety of medium under both aerobic and anaerobic conditions. Certain growths have at times resulted, but none that could be legitimately classed as actinomyces. While Koch's dictums have on one or two occasions been fulfilled in actinomycotic infection, the original growths were obtained from pus. It would be more conclusive if the original cultures had been obtained from granules washed in physiologic solution of sodium chloride.

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DR. ROBERT A. STEWART (by invitation), San Francisco: I feel that one should be careful about the diagnosis of actinomycosis because one can show that many species of actinomyces are normal inhabitants of the mouth and alimentary tract. There are many varieties of these organisms. It is important, from the standpoint of diagnosis and treatment, to establish the type of organism present.

DR. PAUL D. FOSTER, Los Angeles: Dr. John F. Kessel and I have attempted to culture the organisms of actinomycosis. It seems that they are anaerobic in many cases and must be cultured under anaerobic conditions. We have succeeded under vacuum.

DR. H. V. ALLINGTON, Oakland, Calif.: I know that Dr. Templeton first felt that this condition was probably a reaction about a sinus from an area of osteomyelitis secondary to the extraction of a tooth. Roentgenograms were taken with this in mind, however, and no evidence of such a focus was found. Studies with iodized poppyseed oil were not made.

NOTE.—Subsequent roentgenograms made by Dr. A. C. Siefert, Oakland, Calif., with a metal probe in place and after injection of iodized poppyseed oil, showed no connection between the sinus and the mandible, which appeared normal. Further attempts at culture by Dr. Robert A. Stewart were unsuccessful. Another trial with sulfanilamide resulted in no change. Recently the area was radically destroyed by curet and cautery.

A Case for Diagnosis (Telangiectasia Macularis Eruptiva Perstans?). Presented by DR. H. J. TEMPLETON, Oakland, Calif.

R. H., a white American aged 50, was presented before the San Francisco Dermatological Society on Sept. 15, 1939 (ARCH. DERMAT. & SYPH. **41**:994 [May] 1940). There has been no change in the condition since that time.

DISCUSSION

DR. NELSON PAUL ANDERSON, Los Angeles: I think that this patient is the first one with this condition that I have seen and probably one of the first presented in this country. When Weber coined this name in presenting similar cases before the Section on Dermatology of the Royal Society of Medicine, most of the English dermatologists felt that the condition was a rare type of telangiectatic urticaria pigmentosa.

DR. STANLEY O. CHAMBERS, Los Angeles: I should like to suggest the diagnosis of urticaria pigmentosa with telangiectasia. This picture has been seen before.

DR. WILLIAM H. GOECKERMAN, Los Angeles: I have never seen this picture before.

DR. THOMAS J. CLARK, Oakland, Calif.: I asked the patient particularly about the itching, and he said that there was definite itching at times.

Tuberous Sclerosis Syndrome (Epithelioma Adenoides Cysticum, Recklinghausen Disease and Epilepsy). Presented by DR. ARNE E. INGELS, San Francisco.

W. A., a Mexican boy aged 14, entered the Stanford University Hospitals two years ago. He was born with the aid of forceps after twenty-four hours of hard labor. It was thirty minutes before he cried, and he was "blue" for three hours. He had no convulsions.

Development was retarded. He sat at the age of 6 months, walked at 16 months and talked at 4 years. He started school at 7 years but after five years was still in the first grade. He cannot read but likes pictures. He does fairly well with modeling clay.

He has had measles and "flu" but, according to his father, has always been healthy and has had no serious illnesses. A tonsillectomy and adenoidectomy were performed at the age of 4 years.

His family history is noncontributory.

Red spots were noticed on the boy's face soon after birth. These have slowly grown in size and extent. Generalized epileptic attacks began at the age of 1 month and occurred about six to eight times a day. At the age of 1 year and 4 months he was seen by a physician, who prescribed phenobarbital, and he had no more convulsions for three years. From that time he had but few convulsions, until the age of 13, when they became more frequent. However, instead of involving all of his body, they were localized on the left side of his face. During the attacks his head turned to the left, as did his eyes, and the left corner of his mouth was drawn up. In 1937 the boy was seen here and hospitalized. Biopsy specimens of the skin were taken; air encephalograms were made, and various laboratory procedures were done.

At present lesions typical of epithelioma adenoides cysticum are present in a butterfly distribution on the nose and cheeks. On the forehead and back are several typical lesions of neurofibromatosis. Areas of vitiligo are present on the back. There are dry, scaling, red, slightly raised, crusted lesions on the buttocks that do not itch.

The eyes show moderate myopia. In both fundi are found single large, white, raised lesions, about the size of optic disks. These are shaped somewhat like bee hives and are 6 to 8 D. high. The retinal vessels and optic disks appear normal.

The knee and ankle jerks are slightly increased on the left, and the Babinski reaction on the left is positive.

A blood count showed 5,800,000 erythrocytes, 95 per cent hemoglobin and 4,120 leukocytes. The urine and feces were normal. The intelligence quotient was 42. Sedimentation rate was 7 mm. per hour (Wintrobe). The cholesterol content of the blood amounted to 113.6 mg. per hundred cubic centimeters. The reaction to a tuberculin test with a dilution of 1 : 2,000 was strongly positive. The result of a Congo red test was normal. The dextrose tolerance curve was normal. An electrocardiogram showed a few ventricular premature beats but was otherwise normal. Wassermann reactions of the blood and spinal fluid were negative. The spinal fluid was clear and showed no cells or increase in protein, and the colloidal gold curve was 1111100000. Roentgenograms showed areas of calcification scattered over the brain and protruding into the lateral ventricles. Roentgenograms of the hands, arms, feet and legs were negative for cystic osseous changes and periosteal thickening.

Microscopic examination confirmed the diagnosis of epithelioma adenoides cysticum and neurofibromatosis.

Tuberous Sclerosis Syndrome. Presented by DR. ARNE E. INGELS, San Francisco.

D. E., a white girl aged 12 years, entered the children's ward of Stanford University Hospitals on Dec. 13, 1939 because of epilepsy and cutaneous lesions on her face. The latter began at birth and consisted of brownish red papules embedded in the skin. Some appear as small hemangiomas; others combine to form dense plaques. These are found in a butterfly distribution on both cheeks, the nose and the forehead. One lesion, in the right nasolabial fold, is paler than the other plaques, but the surface appearance is the same. This may be the Recklinghausen type of lesion seen mixed with epithelioma adenoides cysticum in some cases. She also shows lesions of acne and seborrhea on the face, which began about three years ago and have resisted treatment.

The patient's mother, aged 35, is confined to Agnews State Hospital, Agnew, Calif., with a "nervous breakdown." There are no brothers or sisters. An aunt died of malignant melanoma, and a grandmother died of cancer.

The details of development are not known. There were no convulsions at birth.

She has worn glasses about two years. The fundi are clear, and the disks are flat. The pupils react normally. She has occasional frontal headaches. "Dizzy spells" began at the age of 3 years. They last four or five minutes, and the patient remembers little or nothing about them.

The patient is in the high seventh grade, but recently, because of too many seizures, she has had to withdraw from school. She always received good grades. She has been using "white pills" continuously. Recently the epilepsy has improved under dietary management.

A neurologic examination gave essentially negative results. The reflexes were all present.

A blood count was normal. The Wassermann reaction of the blood was negative. The spinal fluid was normal. A reaction to a tuberculin test with a dilution of 1:2,000 was negative. The feces were normal. A vaginal smear was negative. The basal metabolic rate was —22 per cent.

Encephalograms on December 15 showed evidence of abnormal suppression of cortical function in both frontal regions and a focus of origin of petit mal waves in the left frontal region.

Roentgenograms of the skull showed digital markings of the inner table of the skull a little deeper than they should be normally. The sutures, however, were not widened. An area of calcification several millimeters in diameter was seen on the right side near the midline, about 3 cm. directly above the right clinoid process. The pineal gland was not calcified. No other calcifications were seen within the brain. This area of density could be within a hemangioma in the brain.

A sugar tolerance test showed the following results: fasting specimen, 90.9 mg.; one-half hour, 147 mg., and one hour, 126 mg., per hundred cubic centimeters.

Encephalograms on Jan. 3, 1940 showed air in the ventricles and a normal appearance and distribution of the subarachnoid spaces.

The mental age was 11 years and 8 months. The intelligence quotient was 93 (average).

Microscopic study confirmed the diagnosis of epithelioma adenoides cysticum and changes of neurofibromatosis.

DISCUSSION ON THE TWO CASES OF TUBEROUS SCLEROSIS SYNDROME

DR. STUART C. WAY, San Francisco: I think that Dr. Ingels has presented 2 excellent examples of so-called Pringle's disease, or adenoma sebaceum.

DR. ARNE E. INGELS, San Francisco: I think it is of enormous importance that sections of certain lesions in both cases show characteristics of epithelioma adenoides cysticum, together with neurofibromatous tissue directly underneath. This fibrous tissue contains nerve fibers, as required in the diagnosis of Recklinghausen disease. No one has been able to demonstrate this previously. Vogt and Vogt, of Norway, one an eye specialist and the other a neuropsychiatrist, have tried to correlate the epithelioma adenoides cysticum and neurofibromatous lesions with Recklinghausen disease. Kveim, of Oslo, Norway, has reported 6 cases of tuberous sclerosis studied extensively (including histopathologic and roentgenologic examinations) and arrived at the conclusion that the fibromatous lesions did not contain nerve elements. The whole series was examined with this particular in mind.

I reported these 2 cases in order to point out and demonstrate the occurrence of nerve elements in the fibromatous lesions, i. e., the neurofibromatous character.

A Case for Diagnosis (Localized Atrophy of the Skin). Presented by DR. ERVIN EPSTEIN, Oakland, Calif.

This patient was presented before the San Francisco Dermatological Society in September 1938 (ARCH. DERMAT. & SYPH. **39**:565 [March] 1939).

After this presentation the patient was given ten daily injections of a pancreatic preparation (padutin), without effect. She was not seen again until Jan. 5, 1940. At this time, the previously described lesions were unchanged, but there had developed five similar lesions following the course of the right third, fifth, seventh, ninth and tenth thoracic nerves, respectively. These lesions were much softer, and the skin could apparently be moved over some linear, tender, subcutaneous masses. Her general condition was unchanged. Biopsy specimens from both the skin and the subcutaneous tissue of the new lesions showed no significant changes.

Further history was obtained recently to the effect that the patient was born after seven months' gestation. There is also a question of the original lesion being present at birth.

DISCUSSION

DR. SAMUEL AYRES JR., Los Angeles: I should like to suggest that this condition might be panniculitis. It is of long standing. She has a sparsity of lesions, but there is something about the appearance of the lesions that suggests this diagnosis.

DR. ERVIN EPSTEIN, Oakland, Calif.: Of course, the possibility of panniculitis must be given serious consideration. However, it would be unusual for panniculitis to be of linear distribution and to follow the course of nerves or the metameric segments of the body. The histologic examination showed normal subcutaneous fatty tissue. Dr. Weidman, in Philadelphia, after seeing a biopsy specimen, suggested the possiblity of a connective tissue nevus. From what I have seen, that would be the most likely diagnosis at this time. If there were panniculitis or some other inflammatory process there, one would expect to find evidence of it in the sections. The long duration, nearly fifty years, is also against a diagnosis of an inflammatory process.

A Case for Diagnosis (Keloid? Scleroderma?). Presented by DR. MERLIN T.-R. MAYNARD, San Jose, Calif.

H. L. A., a white man aged 65, is presented because of contraction and hardness of the right side of the nose, which has been present for a number of years. He also states that there has been a thin watery discharge on the right side of the nose for some time.

As a young man he did some amateur boxing. He has been a tire salesman and a service station operator and was also on a ranch for twelve years. He has had a habit of rubbing and tweaking his nose for a number of years.

The patient's daughter had a keloid which developed after a severe burn on the back of her hand.

A diagnosis of tertiary syphilis, as first choice, and epithelioma, as second choice, was made. Examination of the inside of the nose showed an area of hardness without ulceration. A Wassermann reaction was negative. After microscopic examination of a biopsy specimen the lesion was considered keloidal. The patient was given four subintensive treatments with roentgen rays filtered through 1 mm. of aluminum at monthly intervals. This produced no change.

The patient is now taking vitamin D, which might have an effect if the lesion is scleroderma.

DISCUSSION

DR. ARTHUR FLETCHER HALL, Santa Monica, Calif.: I should like to suggest the diagnosis of factitia or artefact due to long-continued, self-inflicted trauma.

Multiple Benign Tumor-Like New Growths of the Skin (Schweninger and Buzzi) Associated with Syphilis. Presented by DR. HIRAM E. MILLER, San Francisco.

F. Z., a Mexican-American aged 39, was first seen in the University of California Dermatologic Clinic in February 1934. At that time he had numerous discrete lesions distributed over the trunk and upper limbs. These had been present for one year. The lesions were the size of a quarter, slightly lighter than the surrounding skin and definitely atrophic. He had a small, excoriated papule on the scrotum, which had been there for one week and from which Spirochaeta pallida was identified by dark field examination. He gave a history of a primary lesion of the penis six years previously, for which he had received four intravenous injections. The results of the rest of the physical examination were essentially normal.

Wassermann and Kahn reactions of the blood were both positive on several occasions until May 26, 1937. Since then they have been negative. The spinal fluid on May 12, 1938 was normal.

This patient has had regular antisyphilitic therapy since January 1937. Prior to this he was uncooperative and the treatment had been sporadic.

DISCUSSION

DR. SAUL S. ROBINSON, Los Angeles: I concur in the diagnosis in this case. The atrophic areas and invaginated lesions are typical.

DR. BENJAMIN A. NEWMAN, Los Angeles: During my examination of this patient I noticed that he presented seven or eight pea-sized nodules on the sides of his chest and flanks, of which he was unaware. Evidently these lesions represent the tumor stage of macular atrophy. On top of each of these lesions there is present a pinpoint-sized to pinhead-sized erythematous spot. I think the association of this inflammatory spot with each of these lesions is more than coincidental, and it may represent the connecting link between the two types of primary atrophy.

For ten years, at various conferences and meetings, I have been listening to arguments and discussions concerning the classification of the various types of macular atrophy. In brief, macular atrophy has usually been classified as primary and secondary, the primary consisting of Jadassohn's anetoderma and the Schweninger-Buzzi type. The Jadassohn type is differentiated from the latter by the presence of a surrounding violaceous ring or a preexisting inflammatory reaction, while the latter is unaccompanied by any evidence of inflammation. This patient visibly demonstrates the minimal inflammatory reaction that is necessary to produce the eventual destruction of the elastic fibers and presents an excellent example of the unnecessarily cumbersome classification of this disease. The dermatologic literature would greatly benefit if these esoteric classifications were to be discontinued and all these conditions considered merely macular atrophy, with the name modified only when the etiologic agent is known, e. g., macular atrophy following secondary syphilis.

DR. ARNE E. INGELS, San Francisco: I agree with the last remark. I think, however, that this condition is a distinct disease entity. I remember a patient I saw several years ago who showed the same clinical and pathologic pictures. I agree with the diagnosis.

DR. HIRAM E. MILLER, San Francisco: The classification of this disease is an unsatisfactory and cumbersome one. Dr. Chargin has suggested that the term "anetoderma" (Schweninger-Buzzi type) be used. On examining this patient, some of the men questioned the diagnosis because it was not possible to invaginate most of the lesions. These areas have been present for many years, have become harder and have lost their resilience. When the patient was first observed, the lesions could be readily forced into the underlying tissue.

Hyaloma (Colloid Degeneration). Presented by DR. STUART C. WAY and DR. EDGAR C. HAAG (by invitation), San Francisco.

T., a white French-Basque man aged 45, has lived and worked in the United States for many years as a sheepherder. He consulted me on Jan. 16, 1940, complaining of a nodular eruption which involved the face and dorsa of the hands only, areas exposed to the elements by the nature of his work.

The lesions first appeared on the forehead in 1928 and gradually spread to involve the nose and cheeks and later the backs of the hands. There is no history of his having received medication prior to its onset, nor have the lesions been treated. They have caused the patient no inconvenience except by disfiguration.

The forehead, bridge of the nose, cheeks and backs of the hands are covered with firm, shiny, nodular elevations, varying in size from that of a pinhead to that of a buckshot. They are variously shaped, vesiculoid nodules, yellowish and

translucent. When they are punctured, a clear gelatinous material can be expressed. All other parts of the body appear entirely normal.

A Wassermann reaction of the blood was negative. A blood count and the urine were normal.

Spectroscopic examination of urine for hematoporphyrin showed the amount to be within normal limits. The faintest trace was found.

DISCUSSION

DR. STANLEY C. ANDERSON, Los Angeles: I agree with the diagnosis in this case as presented. There might, however, be disagreement as to terminology. Degenerative products of a clear homogeneous nature may be seen in many body tissues. These can be distinguished from each other by their chemical or staining properties. The term "colloid" is generally reserved for a product of glandular structures, as of the thyroid and glands of the gastrointestinal mucosa, whereas "hyalin" is usually applied to material derived from connective tissue. The term "hyaloma" suggests a new growth.

Pathologically, the lesions are the result of droplets of a clear, gelatinous fluid derived from the degeneration of the collagen bundles and elastin of the cutis and therefore may properly be known as hyaline degeneration of the skin.

DR. STUART C. WAY, San Francisco: The question of terminology is an old one and arises in many cutaneous diseases. Hyaloma is extremely rare, and not more than 25 cases of this condition are believed to have been reported. Many of the patients were outdoor workers and exposed to the elements, an apparently contributory factor.

A Case for Diagnosis (Kaposis Sarcoma?). Presented by DR. ERVIN EPSTEIN, Oakland, Calif.

H. K., a Japanese woman aged 37, acquired pulmonary tuberculosis four years ago, for which she is still receiving pneumothorax therapy. After about one year in the hospital, she noted a pruritic area on the rim of her right ear. A nodule developed on this spot and has been slowly enlarging for the past three years. Since then, two additional nodules have developed close to the original lesion, although all have remained discrete. The patient offers no general complaints. There is no significant lymphadenopathy, splenomegaly or hepatomegaly. Roentgenograms revealed no enlargement of the mediastinal lymph nodes. All laboratory tests have given negative results except for the finding of 6 per cent eosinophils.

One of the nodules was removed, sectioned and stained with hematoxylin and eosin. The epidermis showed no significant alterations. The corium was involved by a dense cellular infiltrate, which spared the papillary layer. The infiltrate consisted of lymphocytes; larger, faintly staining cells with large nuclei containing prominent chromatin networks and mitotic figures; giant cells, most of which presented clumped nuclei in the center of the cells; a few polymorphonuclear leukocytes, eosinophils and plasma cells. There was some vascular dilatation but no evidence of hemorrhage. A prussian blue stain showed no blood pigment.

DISCUSSION

DR. ARNE E. INGELS, San Francisco: The histologic picture of the condition in this case is clearly that of Kaposis disease.

DR. ERVIN EPSTEIN, Oakland, Calif.: I thought that clinically the condition was Kaposi's sarcoma. If so, this case is said to be the first one of the disease reported in a Japanese. As far as the lesions' being in an unusual location on her ear is concerned, Becker and Thatcher (Becker, S. W., and Thatcher, H. W.: *J. Invest. Dermat.* **1**:379 [Oct.] 1938) found 2 cases in which the condition started on the ear. In private practice I have a case of generalized Kaposi's sarcoma with identical lesions on the ears. The occurrence in a woman is another unusual feature of this case.

DR. MERLIN T.-R. MAYNARD, San Jose, Calif.: I should like to suggest the possible diagnosis of leprosy.

Ichthylosis (Embryonic Epitrichial Layer Persistent at Birth). Presented by Dr. Thomas J. Clark, Oakland, Calif.

This girl was born at full term, the twelfth child of the mother, on July 19, 1933. At birth the baby was covered by a membrane comparable to cellophane, which was loosely attached to the skin.

During the first week this epitrichial layer exfoliated. After this, the baby's skin was dry and more reddish than usual. The development and weight were normal, with the exception of scant hair on the scalp and partial growth of the nails of the fingers and toes, half of the nail beds distally being uncovered.

Some difficulty was experienced in taking a bottle feeding for the first forty-eight hours, due to interference with the outside membrane's attachment to the lips.

For the first few weeks the baby's skin was harsh and dry, but there was no scaling suggestive of ichthyosis until she was 2 months of age, when ichthyotic scales on the trunk and thighs appeared.

During the first year of the child's life the exfoliation of the skin from the ichthyotic condition was not uniform, but was excessive at intervals of about one month.

The little girl is now past 6 years of age. She has had measles and whooping cough. She weighs 47 pounds (21.3 Kg.), has a good appetite and is normal except for the ichthyotic skin.

The cutaneous areas affected at present are the scalp, trunk, buttocks and knees. The palms and soles are dry.

The child's mother, now 50 years of age, has normal skin. Of the 12 children born to her, 3 have been ichthyotic: 2 girls and 1 boy. All 3 were born with the embryonic membrane. This child is the only 1 to survive. The other girl and the boy lived only a few days. The child's maternal grandmother gave birth to 16 children, of whom 2 boys and 1 girl were ichthyotic. The child's mother has brothers and a sister who have normal skins.

Pigmented Unilateral Nevus-Like Lentigo. Presented by Dr. Charles Albert Shumate, San Francisco.

R. F., a girl aged 17, was seen at the clinic of St. Mary's Hospital on Jan. 28, 1940. She presented small, dark brown macules scattered over the right side of the forehead, the entire nose, right cheek, right side of the lips and chin and right side of the anterior surface of the neck.

On the lower right eyelid is a dark patch which the mother says has been present since birth. When the patient was about 5 years old this pigmentation began to develop and has been in the present condition since she was 7 years old. Exposure to the sun aggravates the condition but causes few freckles to develop on the left side. The patient sunburns easily.

The patient is presented for advice as to treatment.

DISCUSSION

Dr. Arthur Fletcher Hall, Los Angeles: I should be interested to know if an ophthalmoscopic examination would show abnormal deposits of pigment in the retina of the affected side and none on the other side.

Dr. Charles Albert Shumate, San Francisco: No ophthalmoscopic examination was made.

Dr. Merlin T.-R. Maynard, San Jose, Calif.: From the standpoint of therapy, freezing with solid carbon dioxide would give some temporary beneficial result.

Note.—Ophthalmoscopic examination by Dr. G. E. Nasser, of St. Mary's Hospital, showed no abnormalities of any kind.

Fox-Fordyce Disease. Presented by DR. CHARLES ALBERT SHUMATE, San Francisco.

W. S., a girl aged 17, was seen at the Convent of the Good Shepherd on Jan. 18, 1940, presenting firm, yellowish gray papules in both axillas and, to a less extent, around the vulva and breasts. There is a moderate amount of itching.

The papules appeared in the axillas two years ago and near the vulva and breasts about a year ago.

There is no menstrual disturbance, and except for nervousness the patient's general health is good.

Past treatment at the Mary's Help Hospital has consisted of two roentgen ray treatments, with temporary relief from itching, and electrocoagulation of the papules. These papules have returned.

A complete blood count and urinalysis showed no abnormalities. A Wassermann reaction of the blood was negative.

(Histologic sections were presented.)

DISCUSSION

DR. STUART C. WAY, San Francisco: Very little change has taken place in this patient since I presented her before the society two years ago. Photographs made at that time bear out this impression.

A Case for Diagnosis (Small Necrotic Lesions of the Left Hand and Wrist). Presented by DR. H. J. TEMPLETON, Oakland, Calif.

C. R. N., a white man aged 34, was first seen on Oct. 31, 1939 because of numerous areas of necrosis on the dorsum and sides of the left hand. He states that in January 1938 he burned his left hand with acid while working for a battery company. After this an "infection" of the left hand and forearm developed. This healed after three months. He had no further trouble until about two months prior to entry, when he again burned his left hand with sulfuric acid. After this the present lesions began to develop. They apparently begin about follicular orifices as small, reddish papules, which slowly increase in size and undergo central necrosis. The brownish central necrotic area in some instances has become 1 cm. or more in diameter and is surrounded by a dull, reddish infiltrated margin. No purulent exudate develops; the necrotic center remains dry and adherent to the base of the ulcer, although a fairly sharp line of demarcation exists. Healing takes place, with irregular, firm scarring. The evolution and involution of the lesions are remarkably slow, single lesions lasting from one to three months. At present the active lesions are, for the most part, confined to the radial side of the back of the hand and the volar surface of the wrist. Aside from the involvement of the left forearm in 1938, the eruption has been confined entirely to the left hand and wrist.

The patient works each day in rubber gloves. He does essentially the same work with both hands in inspecting batteries. Every precaution is taken to prevent contamination of his hands with battery acid, and chances of repeated contact with it are decidedly remote. He has not been absent from his work.

Diagnoses of dermatitis factitia and of pyoderma secondary to sulfuric acid burns were considered.

A Kline reaction of the blood was negative. A blood count showed 8,050 leukocytes, with a normal differential count. The urine was normal. The reaction to a tuberculin test was negative. Cultures from necrotic lesions showed a sparse growth of nonhemolytic staphylococci.

There has been slow improvement. There are relatively few lesions present now, although an occasional new one still develops.

Treatment has consisted mainly in long periods of occlusive dressings, with gelatin of zinc. Periods of treatment with hot compresses, dressings of ammoniated

mercury and chlorhydroxyquinoline (quinolor) ointments, lightly filtered roentgen rays and repeated spongings with weak sodium bicarbonate solution have made no notable difference.

DISCUSSION

DR. PAUL D. FOSTER, Los Angeles: The patient says the condition never starts unless he gets acid on his hands. Once in a while the acid gets into his rubber gloves. I should think that would account for the lesions. They certainly could pass for acid burns.

DR. SAUL S. ROBINSON, Los Angeles: I noticed that only a Kline test was done in this case. I suggest that Wassermann and Kahn tests be done to rule out the possibility of syphilis.

DR. MERLIN T.-R. MAYNARD, San Jose, Calif.: The patient says he is left handed and the left hand is the one that comes in contact with the batteries and battery acid. To keep away a volatile substance, occlusive dressings have to be adherent and have to exclude air entirely. The sweat that accumulates under the dressings may absorb volatile fumes and make the condition worse than in open air.

DR. N. N. EPSTEIN, San Francisco: I should like to ask if the patient had a thorough therapeutic test for syphilis.

DR. H. V. ALLINGTON, Oakland, Calif.: He has had no therapeutic test for syphilis.

Cheilitis Exfoliativa. Presented by DR. ARNE E. INGELS, San Francisco.

G. K., a white woman aged 30, came to the office on Jan. 3, 1939. She complained of an eruption of the lips, which had been present for four years. Swelling and crusting occur. When the crusts are removed every third day, a thin, paper-like appearance is left. This cycle is repeated regularly, without any actual soreness of the lips. Various lipsticks, tooth powders and mouth washes were used, and patch tests with these gave negative results. Smoking was stopped for a long time but did not make any difference in the picture. Smoking was then resumed, without any aggravation.

The patient is apparently healthy. There are no infected teeth or tonsils. The patient had no other cutaneous symptoms or obvious evidence of seborrheic dermatitis. The Wassermann reaction of the blood was negative.

The patient was pregnant when first seen. After childbirth the condition was not changed.

Treatment has included use of vitamins, roentgen rays and mild stimulants locally. The condition cleared completely for two months but subsequently relapsed.

At present the lip does not show the heavy crusting often present.

DISCUSSION

DR. SAMUEL AYRES JR., Los Angeles: I have 2 patients under my care at present with an identical type of lesion. In both cases the scaling is confined to the upper lip along the line of junction of the cutaneous and the mucous surface. Both patients have a moderate amount of seborrheic dermatitis of the scalp, and a possible relation between this type of cheilitis and seborrheic dermatitis has previously been pointed out. Both patients have been more or less resistant to treatment, although showing temporary improvement under fractional doses of roentgen rays and sulfur and salicylic acid ointment.

DR. HIRAM D. NEWTON, San Diego, Calif.: In a few cases I have observed beta rays of radium have produced a mild reaction and left a satisfactory smooth lip.

DR. MERLIN T.-R. MAYNARD, San Jose, Calif.: I have a patient with similar cheilitis who has almost complete obstruction of the nose. She wakes up in the morning with her mouth dry from sleeping with her mouth open.

Dr. Ingels' patient also has almost complete obstruction of the left side of her nose. She sleeps on her back and finds her mouth dry in the morning. I suggest that a chin strap be worn at night.

Subacute Lupus Erythematosus. Presented by DR. ARNE E. INGELS, San Francisco.

C. L., a white woman aged 39, was presented before the San Francisco Dermatological Society as a patient with lupus erythematosus on April 21, 1939 and again at the meeting of September 15 (ARCH. DERMAT. & SYPH. **41**:436 [Feb.], 987 [May] 1940).

Since her last presentation, the patient has continued bismuth therapy. The lesions on the nose and lip, as well as her general condition, have shown progressive improvement.

Multiple Idiopathic Hemorrhagic Sarcoma (Kaposi's Disease). Presented by DR. WILLARD M. MEININGER (by invitation), San Francisco.

E. R., an Italian laborer aged 69, who has been in the United States since the age of 20, first noticed a black spot on the medial aspect of his left ankle eight months ago. It gradually increased in size, and similar new areas appeared on his toes and fingers. He complains of considerable itching of only the first patch, and his toes feel frozen.

He had malaria and yellow fever in childhood. Gonorrhea and soft chancre developed in 1900. An appendectomy was performed in 1915. An attack of severe epigastric pain in 1932 was diagnosed as peptic ulcer. Since then he has maintained a smooth diet, though symptoms have never recurred. He has had tinnitus for twenty-five years.

There are bluish red to dark brown nodules and slightly elevated and fairly well marginated plaques on the hands and feet. Hyperkeratosis is present on the feet, and there is pitting edema of the lower extremities. Ill defined, duskily erythematous patches are present on the left ear and lower lip. The fundi, nose and throat are not involved. The results of neurologic examination were normal.

Examination of the blood showed 5,550,000 erythrocytes and 16.6 Gm. of hemoglobin per hundred cubic centimeters (97 per cent). There were 11,750 leukocytes, with 74 per cent polymorphonuclear neutrophils, 20 per cent lymphocytes and 6 per cent monocytes. The urine was normal. The Wassermann reaction was negative. A roentgenogram of the chest was normal. Microscopic study of a biopsy specimen showed a typical picture of Kaposi's disease.

No evidence of visceral involvement has been found.

METROPOLITAN DERMATOLOGICAL SOCIETY

JOSEPH C. AMERSBACH, M.D., *President*

THOMAS N. GRAHAM, M.D., *Secretary*

New York, April 15, 1940

Arsphenamine Dermatitis. Presented by DR. HENRY D. NILES.

E. S., a colored woman aged 43, was born in the British West Indies. Eight years ago she was given eleven intravenous injections of silver arsphenamine for arthritis. She complained of itching after the third injection. Although swelling and dermatitis occurred after the third injection, treatment was continued. She was admitted to the New York Hospital with generalized, exfoliative dermatitis.

Biospectric examination of a piece of affected skin showed no silver but an increased arsenic content. Histologic examination showed dermatitis. For the past three or four years she has had many forms of therapy, including roentgen irradiation, injections of sodium thiosulfate and calcium gluconate, administration of vitamins and sedatives and varied topical applications, with little relief of the

itching and with no improvement in the cutaneous manifestations. Examination reveals large areas of pigmented, lichenified skin with small areas of normal skin, chiefly on her nose and on the flexor surfaces of her forearms. The itching is intense, and she is presented for suggestions as to therapy.

DISCUSSION

DR. LESLIE P. BARKER: I think that the condition in this case is definitely arsphenamine dermatitis and is not due to silver. Although the patient has not had injections of arsphenamine for some time, she could easily have gotten more arsenic from vegetables or fruits, and she should have determinations of the arsenic content of the blood and of the affected skin. Silver arsphenamine was used rather extensively at one time for arthritis, although I do not believe it has been very successful in that disease.

DR. LAIRD S. VAN DYCK: I have seen a similar condition following injection of gold salts. Gold is being administered for arthritis rather than silver nowadays. I believe metal therapy for arthritis should be discarded on account of the many unfavorable reactions which are seen.

DR. MAURICE J. COSTELLO: What was the response to roentgen therapy? I agree with Dr. Van Dyck as to the danger of metal therapy for arthritis, especially when 50 mg. doses of gold sodium thiosulfate are exceeded.

DR. RICHARD J. KELLY: I agree with the diagnosis.

DR. HENRY D. NILES: Of interest regarding this patient is that she has had repeated negative Wassermann reactions and silver arsphenamine was given for arthritis, not for syphilis. She complained of itching and swelling and dermatitis after the third injection, but she had eight more after that, so that when I saw her she had to be hospitalized for generalized acute exfoliative dermatitis. She almost died in the first few days. She has had almost every conceivable form of therapy. She has hay fever but had no eruption until after the course of silver arsphenamine. I agree with what Dr. Kelly said, and I have heard several comments on the fact that when arsphenamine is given for some condition other than syphilis it is far more likely to cause a reaction than when it is given for syphilis. Similarly, gold sodium thiosulfate given for vitiligo causes many more ill effects than when used for lupus erythematosus or tuberculid. It is hard to explain this increased toxicity of a drug when employed in treatment of diseases other than the one for which it was intended.

A Case for Diagnosis (Keratosis Seborrhoeica?). Presented by DR. HENRY D. NILES.

M. R., a white woman aged 57, was first seen today. She presented on the center of the tip of the nose a roughly round patch the size of a large pea, which was covered with thick yellow greasy scales. On removal of the scales the center of the lesion was slightly red, indurated and spongy, surrounded by a flat, red ring.

On Feb. 11, 1929 a single application of 30 mg. of radium filtered with 0.3 mm. of platinum was applied to the lesion, giving a dose of 600 r.

The patient states that the scales reform within a week after removal but that the lesion gives no sensation.

DISCUSSION

DR. ROYAL M. MONTGOMERY: In view of the facts that the diagnosis seems to be a little obscure and that there is scarring present, I suggest biopsy of a small specimen to determine the diagnosis. The biopsy scar would be negligible.

DR. LESLIE P. BARKER: I do not know what this lesion is. It appears to be a scar and not an epithelioma. I think it would be dangerous to use large doses of roentgen rays on this area, as the cartilaginous part of the tip of the nose is covered only by a thin scar and radiation would probably result in ulceration. I certainly should not treat the lesion unless the patient would submit to a biopsy.

DR. LAIRD S. VAN DYCK: The lesion seems to be mostly scar tissue, and I think it is impossible to make a definite clinical diagnosis from the present appearance.

DR. THOMAS N. GRAHAM: I think that the lesion may be a keratosis which has had some treatment. I should also consider the possibility of a basal cell epithelioma, although the lesion certainly is not typical of either condition.

DR. MAURICE J. COSTELLO: I think that this patient has a precancerous keratosis. Taking a specimen for biopsy from this location always increases the scar. I should destroy the lesion by electrodesiccation and with a sharp curet.

DR. RICHARD J. KELLY: I feel that the lesion is not an epithelioma. The edges of the lesion are soft. The duration is eleven years. In that time she would have had considerably more destruction than she has now if the lesion were an epithelioma. The edges would show a pearly margin, which they do not show at the present time. I think the lesion is factitious. I do not see the point in treating this lesion with roentgen rays, since the scarred area is large and lies directly over cartilage. A biopsy should be done before any therapy is instituted.

DR. JOSEPH C. AMERSBACH: I do not think the lesion can be diagnosed as malignant. This question could be solved by using a curet to see if the tissue is friable or by doing a biopsy.

DR. HENRY D. NILES: My impression is the same as Dr. Graham's. I had the advantage of seeing the lesion with the crust on it. It looked like a seborrheic keratosis, with a thick, greasy, yellow scale and a more or less granulomatous, warty base. The superficial scales came off without bleeding or pain. I agree with Dr. Kelly that it is most unlikely that an epithelioma could be present eleven years and have no ulceration or raised indurated border. There is a question in my mind as to therapy and whether or not a specimen for biopsy should be taken from that location. I do not think the patient would let me make a scar or a wound which would require a dressing for a week or two. I am rather determined to treat the lesion with roentgen rays, but there is the question of what dose should be given when the diagnosis is undetermined.

Pityriasis Lichenoides et Varioliformis Acuta. Presented by DR. THOMAS N. GRAHAM.

J. S., a white woman aged 22, was presented at the March 1940 meeting of this society (ARCH. DERMAT. & SYPH. **43**:196 [Jan.] 1941). She has returned tonight in order to show the results of therapy. She has been given an erythema dose of ultraviolet radiation each week. There has been no other treatment. Two biopsy specimens were taken, and the observations were consistent with the diagnosis of pityriasis lichenoides et varioliformis acuta.

Sections showed practically normal epidermis with a widening of the follicle openings. In this area the thick scale was parakeratotic. There was slight edema of the basal cell layer. The blood vessels in the upper part of the corium were dilated and in places surrounded by a moderate round cell exudate. There was no suggestion of vesicle formation.

Further sections showed about the same change with the exception that at the follicle openings there was less thickening. There was some swelling in the prickle cells.

DISCUSSION

DR. HENRY D. NILES: The appearance of the eruption is different from that of last month. Dr. Machacek said that if he had ever seen it before and did not know the history he would make a diagnosis of lichen planus. For a moment tonight I had forgotten that I had previously seen this patient, and I agree that now the clinical picture is that of lichen planus.

DR. ROYAL M. MONTGOMERY: I think this case is one of lichen planus. There are some typical linear, papular lesions that one sees in lichen planus.

DR. LAIRD S. VAN DYCK: I should like to see this patient again in a month or two to determine whether the pigmentation fades out. I never saw so much pigmentation in a case of pityriasis lichenoides.

DR. MAURICE J. COSTELLO: When the patient was presented last month my diagnosis was lichen planus. The lesions seem to have undergone spontaneous involution. I still think, in spite of the histologic diagnosis, that the patient had acute generalized lichen planus. In pityriasis lichenoides et varioliformis acuta constitutional symptoms are likely to be present at the onset of the disease and when new crops of vesicles appear. Vesicles were not seen at any time, which does not favor the diagnosis of the presenter.

DR. LESLIE P. BARKER: Clinically, I think this case is one of lichen planus.

DR. RICHARD J. KELLY: I thought the condition in this case was lichen planus from the appearance of the lesions when the patient was first presented. At present the lesions are even more characteristic. The condition seems to be that type of lichen planus in which the diagnosis is obscure at the beginning but becomes more apparent as the disease progresses.

DR. JOSEPH C. AMERSBACH: The lesions when the patient was first presented were more typical. I think the diagnosis should be proved by biopsy.

DR. THOMAS N. GRAHAM: Since the last meeting I performed two biopsies. The histologic picture did not resemble lichen planus at all but was consistent with parapsoriasis varioliformis. The papules were elevated when the patient was presented last month, but since then the eruption has been practically macular, with nothing left but pigmentation and a few papules on the dorsa of the hands. I think the histologic picture, the absence of pruritus, the absence of lesions on the mucous membrane and the response to ultraviolet radiation establish this case as one of parapsoriasis varioliformis. I do not understand how any one can make a diagnosis of lichen planus or of any other dermatosis from residual pigmentation. At the last meeting, when the eruption was at its height, only two of the members disagreed with the diagnosis of pityriasis lichenoides et varioliformis acuta. At that time there was no histologic study to rule out lichen planus.

Follicular Tuberculid. Presented by DR. THOMAS N. GRAHAM.

F. P., a white woman aged 26, has had discrete, small, violaceous papules on the legs, just above the ankles. The lesions are somewhat indurated and slightly tender on pressure and are of three months' duration.

The patient has had pulmonary tuberculosis since 1934 and tuberculous cervical adenitis. She gives a history of having had erythema induratum at the age of 15, which lasted a number of years. There are some scars still present. She had "tuberculosis of the eyes" between the ages of 8 and 12 years and was treated at the Manhattan Eye and Ear Hospital.

Histologic examination showed a large amount of granular, almost caseous necrotic material near the hair follicles. There was one area suggestive of a tubercle. A few fairly large cells were observed, and occasional giant cells were present. Lymphocytes were scattered about, and although there was no definite area of caseation or typical tubercles, the picture was that of a follicular tuberculid.

DISCUSSION

DR. HENRY D. NILES: I saw this patient at the hospital, and without knowing the history at first I did not make this diagnosis. In view of the history, the presence of pulmonary tuberculosis, the histologic picture and the absence of lichen planus elsewhere, I accept the diagnosis as presented. If the condition is a tuberculid, I do not know just what type it would be, as Dr. Graham has said.

DR. MAURICE J. COSTELLO: The patient has various manifestations of tuberculosis: pulmonary tuberculosis, tuberculous keratitis, cutaneous tuberculosis and cervical tuberculous lymphadenitis. She also has a family history of tuberculosis.

The eruption on the legs is a papulonecrotic tuberculid approaching Bazin's disease in type. I believe one must discard the old idea that pulmonary tuberculosis and cutaneous tuberculosis do not coexist. It is important that patients with cutaneous and other forms of extrapulmonary tuberculosis and members of the same household be examined for pulmonary tuberculosis by roentgenograms of the chest. At times 1 member of a family has erythema induratum while another has pulmonary tuberculosis. I suggest rest in bed for patients with papulonecrotic tuberculid and erythema induratum.

DR. LESLIE P. BARKER: I believe the condition in this case fits in with the erythema induratum group. There are many gradations of the tuberculids ranging from papulonecrotic tuberculid to erythema induratum. It is difficult to classify each condition under an exact clinical entity.

DR. RICHARD J. KELLY: I agree with Dr. Costello and Dr. Barker. My impression is that the condition is a papulonecrotic tuberculid associated with Bazin's disease.

DR. THOMAS N. GRAHAM: I think that the color and induration are suggestive of a tuberculid, although the lesions do not correspond clinically with any type described in the literature. They resemble more closely papulonecrotic tuberculid without central necrosis. The diagnosis of tuberculid is, of course, established by the microscopic observations.

Fox-Fordyce Disease. Presented by DR. MAURICE J. COSTELLO.

M. P., a white girl aged 18, from St. Clare's Hospital dermatologic clinic, presents a follicular, papular eruption in both axillas, confined to the hairy areas. The condition is of nine months' duration. No other member of her family is similarly affected. The follicles are flesh colored, elevated and conical. Itching is not present. There are no similar lesions on the areolas, umbilicus or pubes.

DISCUSSION

DR. HENRY D. NILES: I consider this condition to be early Fox-Fordyce disease, but histologic examination is necessary to confirm this diagnosis.

DR. LAIRD S. VAN DYCK: I think the condition in this case is suggestive of early Fox-Fordyce disease, although the papules seem to be colorless. The absence of itching and inflammation makes this diagnosis a little doubtful, unless confirmed by histologic examination.

DR. LESLIE P. BARKER: I think a biopsy specimen should be taken in order to make a positive diagnosis in this case. Intense itching is a characteristic of Fox-Fordyce disease, and its absence in this case is most unusual.

DR. MAURICE J. COSTELLO: Is the histologic picture of this condition typical, or is clinical information necessary in making the microscopic diagnosis?

Alopecia Areata (Bandlike). Presented by DR. RICHARD J. KELLY.

M. K., a girl aged 11 years, presents a bandlike area of alopecia, extending directly across the vertex of the scalp. The lesion is approximately ½ inch (1.3 cm.) in width and is of two months' duration. The child's mother states that it appeared suddenly one morning after the application of a tight rubber band ½ inch in width which had been applied to keep the patient's hair in place overnight.

DISCUSSION

DR. ROYAL M. MONTGOMERY: I think this case is an unusual one of alopecia areata in linear formation. I have never encountered any like it before.

DR. LAIRD S. VAN DYCK: I think this case is rare enough to be worth reporting. I never have observed a case in which the alopecia followed a line

transversely across the scalp. The history of the patient going to bed with a headache and wearing an elastic band around her head all night makes one wonder if alopecia areata is due to temporary interference with the blood supply in the area of hair loss.

DR. THOMAS N. GRAHAM: I have never encountered a case like this. I thought there were some hairs in the area of alopecia but presume that they have grown in since the onset of the condition.

DR. MAURICE J. COSTELLO: This condition should be referred to as the ophiasic type of baldness, which occurs in streaks or bands. The child's hair was dressed in tight braids beginning at either extremity of this area of baldness. Ophiasis has been reported following prolonged tension on the hair, such as occurs when the hair is put up in crimpers at night. It is not uncommon to observe this condition in Negresses whose hair was dressed in this manner in childhood.

DR. RICHARD J. KELLY: When first seen, this girl had a band 3/8 to 1/2 inch (1 to 1.3 cm.) in width directly across the scalp with definite loss of hair and the typical appearance of alopecia areata. I think the clinical picture was a bit obscured tonight because of therapy.

Linear, Cavernous Hemangioma. Presented by DR. RICHARD J. KELLY.

C. C., a Negress aged 35, is presented because of a unilateral cavernous hemangioma of the right arm and forearm, extending from the shoulder to the wrist, on the flexor surfaces. One area of the lesion has been treated with radium, and several other areas are under treatment with solution of quinine hydrochloride and ethyl carbamate (urethane).

DISCUSSION

DR. JOSEPH C. AMERSBACH: I should like to see this patient at some future day if she is kept under treatment. One might sclerose one of the main vessels and produce blockage in this type of case.

DR. HENRY D. NILES: The interesting feature to me in this case is that so many areas have bled with slight trauma and become dried, almost black, and crusted. A hemangioma is certainly unusual in a person of her age. The lesions are so active, even in an adult, that I think there might be some chance of their responding to radium as well as to injections. With such an extensive lesion one could treat one area with injections and one with radium for purposes of comparison and perhaps another with solid carbon dioxide. I should try out several methods, since the condition is so extensive, and see which one works the best.

DR. ROBERT R. M. MCLAUGHLIN: Has Dr. Kelly had much success with cavernous hemangiomas by the injection treatment?

DR. THOMAS N. GRAHAM: I think that the more superficial lesions might respond better to treatment with solid carbon dioxide with a better cosmetic result. Of course the injection method is a better kind of treatment for the more deeply seated lesions.

DR. MAURICE J. COSTELLO: I believe that this patient would do better without treatment. She has had this condition all her life, thirty-five years, and it has never bothered her. One cannot hope to cure such an extensive process with sclerosing agents. If the deep lesions were injected one might encounter trouble. Even keloids, which are common in the Negro, might develop. An increase in the size of the bones on roentgen examination has been found in such cases. Clinically, the enlargement of the bones of the affected extremity is evident in this case. I believe the diagnosis of this condition is Parkes-Weber disease (Cuero, R.: La hemangiectasia hipertrofica de Parkes-Weber, *Arch. de med. inf.*, 1936, vol. 2).

DR. RICHARD J. KELLY: I have presented this case because of the unusual distribution of the lesions and also because the condition is an illustration of a hemangioma which has remained present long after its appearance at birth. This patient has had radium therapy of only one of the small lesions on the flexor surface of the forearm, about 3 inches (7.5 cm.) above the wrist. The other lesions are being treated by injection of quinine hydrochloride-ethyl carbamate (urethane) solution. I believe that injection therapy is the method of choice here and can be given with perfect safety if it is done over a long time. It has been suggested that infra-red photographs be made of the lesion. These have been made but show nothing striking.

BRONX DERMATOLOGICAL SOCIETY

MARION B. SULZBERGER, M.D., *President*

HENRY SILVER, M.D., *Secretary*

May 23, 1940

Early Syphilis Treated with Neoarsphenamine by the Intravenous Drip Method. Presented by DR. LOUIS CHARGIN and DR. WILLIAM LEIFER (by invitation).

J. C., a Negro aged 24, was admitted to the Mount Sinai Hospital on July 15, 1938 with a chancre of the penis. The dark field examination showed spirochetes. From July 16 until July 20, inclusive, the patient received a total dose of 4.2 Gm. of neoarsphenamine by the intravenous drip method.

Serologic examinations on July 15 at the laboratory of the New York City Department of Health showed a 6 plus Wassermann reaction. At the laboratory of the United States Public Health Service the result of a Kline exclusion test was 4 plus and that of a Kline diagnostic test was 4 plus; the Kahn standard test gave a 4 plus reaction, and the result of a Kolmer complement fixation test was 44444. On July 22 the results of serologic examinations were essentially the same except that the titered Wassermann reaction had risen to 7 plus. The patient was not seen until March 27, 1939, at which time all the tests previously performed were repeated, and the results were entirely negative. After that the patient was not seen until September 13, at which time the results of all serologic examinations were again negative. From then on he was seen regularly at monthly intervals; at each of these visits complete serologic studies were made, and the results were found to be negative. The last examination was made in April 1940. On March 27, 1939, about eight months after the treatment was given, examination of the spinal fluid in the same laboratories gave negative results.

During the period of observation repeated physical examinations and clinical studies of the blood and urine showed no abnormalities.

Early Syphilis Treated with Mapharsen by the Intravenous Drip Method. Presented by DR. LOUIS CHARGIN and DR. WILLIAM LEIFER (by invitation).

K. A., a white man aged 48, was admitted to the Mount Sinai Hospital in November 1938 with a chancre of the penis and a generalized papular syphiloderm. He was treated by the intravenous drip method and received a total dose of 0.6 Gm. of mapharsen from November 17 until November 22, inclusive. Serologic examinations on November 17 at the laboratory of the New York City Department of Health showed a 7 plus Wassermann reaction. At the laboratory of the United States Public Health Service (Dr. John F. Mahoney) the result of a Kline exclusion test was 4 plus and that of a Kline diagnostic test 4 plus; the

Kahn standard reaction was 4 plus, and the result of a Kolmer complement fixation test was 44444. On March 3, 1939 the serologic reactions had become negative, and thereafter monthly serologic examinations with all tests until April 1940 have given persistently negative results. On Oct. 31, 1939 an examination of the spinal fluid showed that it was completely normal.

During the period of observation, approximately eighteen months, physical examinations have shown no abnormalities.

Extragenital Chancre Treated with Mapharsen by the Intravenous Drip Method. Presented by Dr. Louis Chargin and Dr. William Leifer (by invitation).

G. B., a Negro aged 25, was admitted to the Mount Sinai Hospital on Feb. 6, 1940, presenting a chancre of the lower lip. Dark field examination of material from the lesion showed spirochetes. The patient was treated by the intravenous drip method from February 7 to February 11, inclusive, during which period he received a total dose of 1.2 Gm. of mapharsen.

Serologic examinations made at the laboratory of the New York City Department of Health on February 7 gave a negative Wassermann reaction. At the laboratory of the United States Public Health Service (Dr. John F. Mahoney) the result of a Kline exclusion test was 4 plus and that of a Kline diagnostic test 4 plus; the Kahn standard reaction was 3 plus, and the result of a Kolmer complement fixation test was 4440. On February 21 serologic examinations made at the laboratory of the New York City Department of Health showed a 6 plus Wassermann reaction; the result of a Kline exclusion test was 4 plus and that of a Kline diagnostic test 4 plus; the Kahn standard reaction was 3 plus, and the result of a Kolmer complement fixation test was 34440.

On March 25 the results of all serologic examinations were completely negative, and they were also negative at the time of the last examination, in April 1940.

DISCUSSION ON CASES OF SYPHILIS TREATED BY INTRAVENOUS DRIP METHOD

Dr. Girsch D. Astrachan: I consider this method of great importance and of great value. There are, however, several problems I should like to clarify. The patients who were observed from one to five years and in whom excellent results were obtained were treated with neoarsphenamine. Then, because of a fatality and a high incidence of polyneuritis, mapharsen was substituted. I am greatly impressed with the usefulness of mapharsen. Dr. Wise and I (*Am. J. Syph., Gonor. & Ven. Dis.* **22**:470, 1938) are of the opinion that mapharsen is preferable to neoarsphenamine in the treatment of late latent syphilis. Dr. Cornell and I (Arch. Dermat. & Syph. **38**:943 [Dec.] 1938) believe that mapharsen is as good as neoarsphenamine in the late stages of congenital syphilis. I am also of the opinion that mapharsen is as efficacious as neoarsphenamine in pregnant women with syphilis. However, I am not certain whether mapharsen is as potent as neoarsphenamine in the early stages of syphilis. The patients treated by Dr. Chargin and his associates with mapharsen were observed for about one year or a little longer, a period too short to determine the permanency of the results. I think that these cases will have to be observed carefully for a few more years before one can decide whether the results obtained from mapharsen equal those obtained with neoarsphenamine. Also, experimental work should be done on rabbits to determine the possibility of permanent damage to important viscera.

I consider this method a big step forward in the treatment of syphilis, and if the results obtained by the authors are confirmed in a large number of cases, this method will play an important role in the eradication of syphilis.

Dr. Adolph Rostenberg: Dr. Chargin and his collaborators deserve a great deal of credit for their excellent work. Of all the devices for a quick cure of syphilis, their method undoubtedly is the nearest approach to Ehrlich's *sterilisatio magna*. The only valid objection in my mind is the question of practicability.

The patient must be hospitalized, and I am afraid that not enough hospital beds will be available for this treatment. I also doubt whether the rank and file of patients will be willing to be confined in a hospital for this disease, as they try to hide their affliction and would rather seek the aid of a private physician or attend a clinic.

DR. LEO SPIEGEL: I believe this method fulfils closely Ehrlich's requirements for a *sterilisatio magna* in a biologic sense and is therefore an important advance since the introduction of arsphenamine. Its use should, however, be limited at least for the present to the early stages of syphilis. I do not believe it has a place in latent syphilis, as the pathologic process differs in the two stages. Furthermore, even in syphilis of one year's duration I doubt whether the results of the treatment would be as effective as in syphilis of seven or eight weeks' duration.

Many, among them Pollitzer, have endeavored to sterilize the patient by giving three full doses of neoarsphenamine on successive days in addition to four injections of a mercury salt. Two or three such courses were given with a rest period of four weeks between courses. The method was not successful, as was shown by the studies of the Cooperative Clinical Group. In Dr. Chargin's work neoarsphenamine was used. It is more toxic than arsphenamine and perhaps accounts for the reactions observed. Old arsphenamine would be my choice in using the drip method. I have not had much experience with mapharsen. This drug, while not as toxic as neoarsphenamine, is perhaps not as effective, according to the latest reports, since a number of recurrences have been observed.

While no animal experimentation has been attempted and the curative dose has not been definitely determined, Dr. Chargin and his associates worked out the dosage, arbitrarily given in five days, so that it approximately equaled in amount the total dosage for three months as recommended by the Cooperative Clinical Group for syphilis in the early stages.

In the 3 cases presented the Wassermann reaction became negative in less than three months. In comparison with statistics of most other observers using other methods this result was quickly obtained. Also, in all the cases so far reported there has been no invasion of the cerebrospinal axis. These favorable results may be due to the greater permeability of the arsenical given by this method, so that the drug not only reaches every tissue of the body but is kept at a high level for a long period.

There have been no speed shock reactions or other unfavorable reactions except those due to the toxicity of the drug. Credit must be given to Hirshfeld, Hyman and Wanger (*Arch. Int. Med.* **47**:259 [Feb.] 1931), who were the first to show that toxic drugs could be introduced intravenously in large quantities by the drip method.

Another great advantage of the method is the economic consideration. The patient is presumably cured in five days, thereby not only reducing the cost of treatment to a minimum but also reducing the many hours which would otherwise be required to obtain a cure by the older methods.

The method is still in the experimental stage and should be used only in institutions equipped for it, under competent observation and for the present in cases of early syphilis.

DR. DAVID BLOOM: Drs. Chargin and Leifer should be congratulated. To me this method of treating syphilis seems to be at least as remarkable and important as the malaria treatment originated by Wagner-Jauregg. The wider use of this method will stimulate further experimentation in regard to dosage and drugs to be used and will also be tried in the different stages of syphilis.

DR. ARTHUR SAYER: What particular reactions in the neoarsphenamine series were so serious as to cause the change to mapharsen in the further investigation of this method of therapy?

DR. CHARLES GREENHOUSE: Will Dr. Chargin give some details as to the action, technic and amount of dextrose used in this method? Also, now that the

authors have had experience with mapharsen and neoarsphenamine, which drug do they prefer?

DR. FRANK E. CROSS: Dr. Chargin discussed this work before this society about three years ago (Chargin, L.: Reinfection in a Patient Treated with Neoarsphenamine by the Intravenous Drip Method, ARCH. DERMAT. & SYPH. **35**: 1169 [June] 1937). I was then greatly impressed with the result. There are few who realize how cautiously this group has attacked the problem, and only by studying the charts can one appreciate the care and thoroughness with which the study has been carried out. Therefore, this treatment should be undertaken only by those who have been trained in this method. With regard to the importance of the method, I can see that years later, when there will be little or no old syphilis and only early syphilis, this method will find its greatest use.

DR. MARION B. SULZBERGER: I think that this method must be recognized as an interesting experiment, and I believe that this is the intention of the presenters. What criteria are necessary to accept this method as successful? It is known that within the first few weeks, or perhaps even within two months following the infection, satisfactory results are obtained with the dose of the arsenical employed by the investigators. It is almost a sterilizing dose as first advocated by Ehrlich. The therapeutic results are no better and no worse than those achieved when large doses of arsenicals were given in short periods to patients who tolerated the drug. In other words, the old results with antisyphilitic drugs were just as good as those in this series, except that the ill effects of the drugs were too great and the administration of massive doses of the drugs had to be discontinued. Many syphilologists have long been giving relatively large doses in a relatively short time. For example, Linser (in Jadassohn, J.: Handbuch der Haut- und Geschlechtskrankheiten, Berlin, Julius Springer, vol. 18, p. 593) administered a total of 4.5 to 6 Gm. of neoarsphenamine in four weeks plus heavy metals. He claimed good results and few ill effects. In examining Linser's statistics it appears that the ill effects with neoarsphenamine are certainly no more and perhaps even less than those encountered in the five day drip treatment method. The evidence suggests that the drip method has not radically reduced the toxicity of neoarsphenamine. It still remains to be seen whether the increased tolerance to mapharsen in the present series is attributable to the drip method of administration, to the excellent intrinsic therapeutic index of the drug itself or to some other factors.

On the other hand, Drs. Chargin, Leifer and Hyman have shown that one can give large doses of mapharsen in a short period of time with relatively little danger. There is, as yet, no proof that the mapharsen was better tolerated because of the method of administration. It appears to me that mapharsen has an excellent therapeutic index in human beings. It will be interesting to see whether this index is not maintained even when mapharsen is given in large daily doses with small syringes and in other ways.

DR. WILLIAM LEIFER (by invitation): The technic is simple and has been previously described (Chargin, L.; Leifer, W., and Hyman, H. D.: *J. A. M. A.* **104**:878 [March 16] 1935. Hyman, H. D.; Chargin, L.; Rice, J. L., and Leifer, W.: *ibid.* **113**:1208 [Sept. 23] 1939). A large number of intravenous infusions of dextrose are regularly given at the hospital, and fever is not encountered. It occurred in former days when the solutions were improperly prepared. Dr. Sulzberger said that one can hospitalize patients with infectious syphilis for two weeks and by routine treatment render the disease noninfectious. I do not think that that can be accomplished. At Bellevue Hospital it is the practice to keep these patients longer than two weeks, but the results obtained with routine therapy cannot be compared with ours. The best statistics published on routine therapy are by Russell (*J. A. M. A.* **114**:1321 [April 6] 1940). He showed that 84 per cent of 6,807 patients with early syphilis disappeared from observation before they had received an adequate amount of therapy to render the disease noninfectious. One hundred per cent of our patients completed treatment. Physiologic solution of sodium chloride was used at the hospital of the Sing Sing

prison for a short period, but it produced pain in the arm, and dextrose as the diluent had to be substituted.

DR. LOUIS CHARGIN: As is known, it is possible to sterilize a rabbit infected with syphilis by a single dose or two doses of an arsenical. The application of commensurate doses to human beings has, however, been found to cause toxic reactions. The intensive methods of Scholtz, Pollitzer (Pollitzer S.: The Principles of the Treatment of Syphilis, *J. Cutan. Dis.* **24**:633, 1916) and others have been found to produce a high incidence of toxicity and required three to eight months of treatment. The Pollitzer method showed satisfactory results in only 23.4 per cent of the cases. The chronic intermittent method requires a year or more of therapy and shows satisfactory results in 65 per cent of cases. The Cooperative Clinical Group method of continuous therapy also requires treatment for one to one and a half years, with satisfactory results in 79.7 per cent of the patients. These percentages pertain to results obtained in early syphilis only.

When Hirshfeld, Hyman and Wanger showed that it is possible by the drip method to administer even toxic agents in large doses, it occurred to me that this method might be an excellent means of treating syphilis. I thought that it might be possible by the slow administration of an arsenical to concentrate the drug and thus approach Ehrlich's *sterilisatio magna*. The reason that 4 to 5 Gm. of neoarsphenamine was chosen as the dose was that this dose approximates the proportionate sterilizing dose for animals. The division of the dose and the treatment period of four to five days were determined by experience. The initial study was carried out with neoarsphenamine. Because of toxic manifestations, like polyneuritis, hepatitis and encephalitis, mapharsen was employed in the last study. The dose of mapharsen was gradually increased to the present level of 1.2 Gm. because it was felt that the best results would be obtained with the largest possible but safe doses. The toxic effects are less frequent and less severe with mapharsen. The serologic tests were, of course, closely followed, and it can be stated that as a general rule the results of the various tests paralleled one another.

With regard to Dr. Astrachan's remarks, it is difficult to judge the value of mapharsen as compared with that of neoarsphenamine administered by routine methods to patients with latent syphilis and with syphilis of pregnancy. In a study that Dr. Leifer, Dr. Rosenthal and I have made in a large series of cases of early syphilis (ARCH. DERMAT. & SYPH. **40**:208 [Aug.] 1939) we have found mapharsen as satisfactory as neoarsphenamine.

With respect to results of treatment during the early stages of syphilis with the intravenous drip method, it may be stated that, while it is yet too early to state definitely, it would appear that the results are about the same with either drug. Our experience to date with neoarsphenamine and mapharsen shows that damage to internal organs is, if anything, less frequent than with routine therapy, if encephalitis is excluded.

In reply to Dr. Rostenberg, I wish to state that the method is practicable and that hospitalization is not a disadvantage but the contrary. It is not necessary to designate the patient's disease. Placing the patient in a hospital takes him out of circulation while he is most dangerous to others.

In reply to Dr. Sulzberger, I must admit I am not acquainted with Linser's intensive method of syphilis therapy. The mixed syringe method (neoarsphenamine and mercury) of Linser is perhaps the least effective of all methods of treatment employed in the early stages of syphilis. I do not think that Dr. Sulzberger refers to this procedure. The drip method differs from the intensive methods of Scholtz, Pollitzer and others in that the drip method consumes less time, is more effective therapeutically, is less toxic and is based on a different principle. With the drip method an attempt is made to maintain a rather high concentration of the arsenic in the body over a prolonged period, in contradistinction to the sudden introduction of large quantities of arsenic, which are rapidly eliminated and so leave the body for comparatively long periods without any effective arsenic.

Lupus Erythematosus Disseminatus. Presented by DR. PAUL GROSS.

S. T., a girl aged 18, was seen at Vanderbilt Clinic on Oct. 25, 1939. The cutaneous eruption began three years ago on the right eyelids and spread rapidly within three to four weeks over the entire face and ears. Two years later an eruption appeared on the fingers. The condition was associated with progressive loss of weight but with no systemic symptoms except for a febrile reaction and flare-up of the eruption following an injection of unknown nature. The patient stated that the eruption became aggravated after exposure to the sun. She had been treated previously with injections of a bismuth and of a gold compound, without benefit.

The eruption involves most of the face and extends to the scalp and ears. There are diffuse areas of erythema with slight infiltration, adherent scales, telangiectases, pigmentation and scattered flat bright red papules the size of a lentil. The eruption is symmetric. The tip and central portion of the nose show definite scarring; the eyebrows are almost completely lacking, and the follicles seem atrophic. On the scalp there are irregular reddish and scaly patches and diffuse areas of alopecia. In the center of the hard palate there is an irregular red lesion with telangiectases and a pale center. On the palmar surface of the end phalanges of all fingers there are circumscribed red scaly lesions with atrophy, which has caused a spindle-shaped deformity of the fingers. Similar lesions are present on the dorsa of the fingers and over the palmar surfaces of several metacarpal phalangeal joints. The balls of the finger tips are free, but under the edge of the nail there are small red and scaly lesions. The periungual area of all the fingers is red, glistening and telangiectatic.

The Kline and Wassermann reactions were negative. Examination of the blood showed 70 per cent hemoglobin and 3,800,000 red cells and 4,000 white cells per cubic millimeter. There was slight anisocytosis. Chemical examination of the blood serum revealed 3.4 mg. of inorganic phosphorus, 9.7 mg. of calcium, 20 mg. of nonprotein nitrogen and 184 mg. of cholesterol per hundred cubic centimeters; there was no bilirubin. There was 9.3 per cent protein, 4.8 per cent albumin, 4.5 per cent globulin and 1.1 per cent euglobulin. The antistreptolysin titer of the blood serum measured 200 units. The ascorbic acid (vitamin C) content of the blood plasma was 0.3 per cent.

The urinalysis showed a 2 plus reaction for albumin and 75 to 80 micrograms of coproporphyrin in twenty-four hours. The roentgenograms of the heart and lungs and the electrocardiogram were normal. Histologic examination showed changes compatible with those of lupus erythematosus. The cozymase content of the blood determined by the factor V for influenza bacilli was extremely low but became normal under treatment, as shown in the following tabulation:

Dilution	Oct. 25, 1939	Nov. 1, 1939	Nov. 22, 1939	Dec. 13, 1939	Dec. 20, 1939	Jan. 12, 1940
1:1,000	—	—	1+	3+	2+	4+
1:2,000	—	—	...	2+	1+	3+
1:4,000	—	—	±	1+	±	2+
1:8,000	—	—	—	—	—	1+
1:12,000	—	—	—	—	—	1+

From Nov. 2, 1939 to Jan. 18, 1940 the patient received liver extract, 8 mg. of riboflavin and 100 to 200 mg. of nicotinic acid amide per day.

The treatment so far has resulted in a gain of weight (12 pounds [5.4 Kg.]), improvement of the anemia, moderate improvement of the cutaneous eruption (especially of the fingers), considerable regrowth of the hair and considerable improvement of the lesion on the mucous membrane. The systematic increase of codehydrogenase to normal values is considered a further indication of clinical improvement.

DISCUSSION

DR. DAVID BLOOM: I believe that the prognosis in this case is poor. Sulfanilamide is contraindicated because of the leukopenia present.

DR. FRANK E. CROSS: I too think the prognosis in this case is unfavorable, in spite of the fact that this woman feels well and is apparently improving. Gold is a dangerous drug in cases of this kind, and when giving it at all one should begin cautiously with doses of 5 mg.

DR. MARION B. SULZBERGER: I notice that Dr. Gross was cautious in labeling the condition lupus erythematosus disseminatus, but he did not state whether he considered it subacute, acute or discoid.

DR. PAUL GROSS: The points that favor the diagnosis of lupus erythematosus with systemic involvement are: (*1*) location of the lesions on the volar surface of the fingers, and particularly the reddish and telangiectatic lesions at the base of the nails, (*2*) definite albuminuria on repeated examination, (*3*) high protein and globulin content of the serum and (*4*) leukopenia and pronounced secondary anemia. Treatment with liver extract and nicotinic acid was indicated because of the extremely low cozymase in the blood. At the Vanderbilt Clinic this therapy has been employed for a number of years, with good results in a number of cases. The most significant response in this case was the improvement in general health and the increase in weight.

Lichen Planus (with Acuminate and Atrophic Lesions). Presented by DR. SAMUEL FELDMAN.

A woman aged 30 presents an itching eruption which has been present for the past four years. On the inner surface of the left thigh just above the knee there is an area about 3 inches (7.5 cm.) square in which numerous dry, globular papules are seen. The area as a whole is somewhat lighter in color than the surrounding skin. There are a few small elevated violaceous patches, their surface slightly scaly and the lines exaggerated. In the younger patches small round papules capped with a horny plug can be seen. Scattered along the anterior surface of the thigh there are a few depigmented areas and a small number of groups of acuminate papules. On the outer surface of the thigh there are atrophic and depigmented spots. A few scattered papules appear to be regressing. On the inner surface of the right thigh there is a receding patch of lichen planus. No lesions are present in the mouth. The condition is accompanied by considerable itching.

Sections were taken from a patch of lichen planus, an acuminate papule and a depigmented area and were examined histologically. The area of lichen planus showed all characters of lichen planus. In addition, there was considerable diminution of the elastic tissue and pronounced edema of the cutis. The specimen of the acuminate papule showed considerable diminution of the elastic tissue and a tendency toward hyaline degeneration of the collagen. The depigmented patch showed flattening of the papillae, diminution of the elastic tissue in the upper layers and fractioning and clumping in the middle layer. There was also hyaline degeneration of the collagen.

Chronic Discoid and Lichenoid Dermatitis in a Woman. Presented by DR. ADOLPH ROSTENERG.

A housewife aged 58 was presented at the March 1940 meeting of this society (ARCH. DERMAT. & SYPH. **42**:987 [Nov.] 1940) with a diagnosis of lymphoblastoma. The reasons for changing the diagnosis are mainly these: The clinical appearance was undergoing changes at various times and several biopsies and examinations of the blood did not reveal the picture of mycosis fungoides or other types of lymphoblastoma.

DISCUSSION

DR. SAMUEL FELDMAN: When I saw this patient at the Bronx Hospital there were no lichenoid or discoid lesions, and the picture suggested erythroderma or perhaps lymphoblastoma. There were three nodules present on the chest, and one

was removed for histologic examination. The biopsy report was chronic inflammation. The nodules disappeared spontaneously, and for that reason they could not be regarded as fibromas.

DR. MARION B. SULZBERGER: It is difficult to accept the suggested diagnosis because of lack of certain essential features. Eosinophilia was practically a constant observation in cases of chronic discoid, lichenoid dermatitis as described by Garbe and me (ARCH. DERMAT. & SYPH. **36**:247 [Aug.] 1937). One feature that is against the diagnosis in this case is the presence of hard subcutaneous nodules, which were not encountered in any of my cases.

DR. ADOLPH ROSTENBERG: I have studied the cases that were reported by Sulzberger and Garbe, and I think that the condition in this case fits in well with their description. I cannot suggest any other diagnosis.

The diagnosis of discoid and lichenoid dermatitis is based on the presence of the following features: The duration of this condition is more than eight years, during which time the diagnosis at various clinics and hospitals was frequently changed because of the variable clinical appearance of the eruption. The outstanding symptom during all this time has been an intractable and uncontrollable pruritus, most severe at night. In favor of the suggested diagnosis is the presence of discoid plaques of varying consistency, infiltrated at times and flattened at other periods of observation, the presence of scaling and of lichenified lesions and the absence of herpetiform efflorescences. The superficial and deeper subcutaneous nodules varying from the size of a small pea to that of a cherry, which appear and disappear at irregular intervals, are painless and show on microscopic exmination the picture of neurofibromatosis, whereas the histologic examination of the skin showed that of eczematoid dermatitis. An unusual feature is the sudden outbreak of perspiration, especially in the region of the neck.

Bullous Fixed Arsenical Eruption of the Mouth. Presented by DR. CHARLES PINES.

C. T., a Negro aged 44, a handyman, has been under treatment at the central social hygiene clinic of the New York City Department of Health for late latent syphilis for the past four years. Three weeks ago after an injection of 0.45 Gm. of trisodarsen (the trisodium salt of 3,3′-diamine-4,4′-dihydroxyarsenobenzine-N,N′-dimethylene sulfonic acid), there developed an eruption confined to the oral cavity. It consisted of moderately distended bullae the size of a pea or of a cherry and was located on the surface of the tongue, on the right buccal mucosa and on the hard palate. Subjectively there was a slight amount of discomfort but no actual pain. The bullae ruptured spontaneously and disappeared completely in two or three days. The patient stated that he had not ingested any drugs.

One week after the lesions of the mouth had healed another dose of 0.45 Gm. of trisodarsen was given. Six hours later the eruption again appeared in the oral cavity. The third injection of trisodarsen was given twenty-four hours ago in order to present the resulting lesions.

Lichenoid Fixed Arsenical Eruption. Presented by DR. LOUIS CHARGIN.

M. M., a woman aged 25, a wool sorter, was admitted six months ago to the central social hygiene clinic of the New York City Department of Health for the treatment of active secondary syphilis. She has been given routine treatment with neoarsphenamine and a bismuth compound. One month ago an eruption developed on the neck, the character of which suggested contact dermatitis. The possibility of its being due to the arsenical, however, was also considered. With that in mind, the patient was given a test dose of neoarsphenamine. On the following day a definite flare-up was observed, limited to the region of the neck. A reaction similar to the one described resulted when mapharsen (0.01 Gm.) was administered.

On the frontal and lateral aspects and the back of the neck there are areas of erythema located around deeply pigmented lichenoid scaly lesions the size of an almond or bean. There is moderate pruritus.

DISCUSSION OF CASES OF ARSENICAL ERUPTION

DR. DAVID BLOOM: In Dr. Chargin's case I wish to suggest that the eczematous eruption on the neck may be due to pediculosis capitis, from which the patient suffers.

DR. WILLIAM LEIFER (by invitation): In the large series of cases of fixed eruptions that Dr. Chargin and I have studied (*J. Invest. Dermat.* **3**:443 [Dec.] 1940) we saw only one fixed eruption of the mucous membrane of the mouth from an organic arsenical. I have perused the work of Abramowitz and Noun, Sulzberger and other investigators and did not find a single report of an eruption of the fixed bullous type from a trivalent arsenical on the mucosa.

DR. MARION B. SULZBERGER: These cases are clinical demonstrations of a fact which Dr. Frank Simon and I proved experimentally some years ago, namely, that, in many cases the so-called "arsenical" eruptions are not due to arsenic (*J. Allergy* **6**:39, 1934). As a rule, the sensitivity is directed to the complex molecule and not to the element arsenic. That is why in some cases neoarsphenamine or mapharsen or another arsenical can be tolerated, in spite of hypersensitivity to some arsenicals. However, occasionally one finds patients who are sensitive to trivalent and not to pentavalent arsenic or vice versa. The animal experiments, along the lines carried out by Simon and me, have again been taken up recently by Miescher (*Dermat. Ztschr.* **78**:313, 1938). He demonstrated that of all the antisyphilitic arsenicals that he studied, mapharsen had the least capacity to sensitize, i. e., the lowest sensitizing index. Moreover, just as Simon and I predicted, the drugs with the lower sensitizing indexes in animal experiments seem to be those least likely to produce human clinical intolerance.

DR. MAX B. KAMPF: In a case of a similar lichenoid fixed eruption under my observation sensitiveness to arsphenamine was found. This patient did not react to mapharsen. It is also of interest to note that small doses of solution of potassium arsenite U. S. P. had no effect on the eruption.

DR. SAMUEL FELDMAN: One of my patients repeatedly had an eruption from neoarsphenamine. When mapharsen was substituted the eruption disappeared, and I was able to continue treatment with that drug for about two years without untoward reactions.

DR. CHARLES PINES: My patient presents somewhat unusual clinical features. However, I feel that the condition is a fixed bullous arsenical eruption, because I was able to obtain a flare-up with neoarsphenamine on two occasions. I was not able to obtain a flare-up with mapharsen.

DR. LOUIS CHARGIN: In the large series of cases that Dr. Leifer and I studied at the department of health we observed that if a patient reacts to one arsenical he usually reacts to most of them.

Lesions produced by one trivalent arsenical may be activated by other trivalent arsenicals and also by some pentavalent arsenicals (acetarsone). Activation has been seen only when the drug is given by the intravenous or intramuscular route. Patch tests and iontophoresis have consistently given negative results. Since all trivalent arsenicals do not activate with equal frequency, it is possible to continue therapy uneventfully by a change of arsenical.

Hypertrophic Scars Following Herpes Zoster. Presented by DR. LEO SPIEGEL.

J. R., a school girl aged 14, was brought to the clinic of the Lenox Hill Hospital presenting an eruption which began the first week in March. At first she complained of severe pain, after which a red spot appeared on the right cheek.

The eruption spread rapidly over the entire cheek and upper lip and was diagnosed as herpes zoster by the family physician. Soon after that the patient and her sister had varicella.

There is an irregular vivid red patch with well defined borders, limited to the right cheek and upper lip. In some parts of this red area elevations appear above the level of the skin which are of various size resembling ridges, plaques and nodules.

DISCUSSION

DR. FRANK E. CROSS: The mother states that the lesions were crusted, and she used tincture of green soap to remove the crusts. Perhaps this method of treatment is a factor in promoting the keloid.

DR. CHARLES LERNER: I think the mother maltreated the lesions by using home remedies, possibly some irritating or caustic applications. As far as treatment is concerned, I think that the administration of unfiltered roentgen ray therapy in small doses should yield a good result, since the scars are not thick.

DR. DAVID L. SATENSTEIN: I cannot accept the theory that the crust formation or the soap is responsible for the hypertrophic scars. Tissue necrosis as a result of herpes zoster is adequate to account for the hypertrophic scars. Even the mildest form of herpes zoster might be followed by a keloid.

DR. MAX B. KAMPF: What is the experience with the use of low voltage roentgen or grenz rays in the treatment of early keloids?

DR. CHARLES LERNER: I have treated many scars with grenz rays, and I do not think that there is any advantage over the usual superficial roentgen therapy.

DR. CHARLES WOLF: There are two factors responsible for the keloids in this case. The keloid tendency of the patient and the external medicaments used. I believe that time and a small amount of roentgen therapy will flatten the lesions.

Kaposi Sarcoma with Low Grade Spindle Cell Sarcoma. Presented by DR. PAUL GROSS.

M. F., a Jew aged 81, was seen at the Hospital for Joint Diseases presenting reddish lesions on the feet, which had persisted for the past two years. About two months ago there developed on the left foot a growth which enlarged rapidly.

On the anterior and lateral aspects of both ankles are several bluish red, somewhat infiltrated patches of firm consistency. The surface of these lesions is slightly scaly and hypertrophic. There is moderate edema of both feet and slight verrucous hyperkeratosis on the dorsal surface of the toes. On the outer aspect of the left foot there is a round, dark red, lobulated tumor, narrow at its base, the size of a large marble. The surface is partly denuded and covered with a grayish bloody exudate. The tumor is firm and slightly tender.

The histologic examination of a specimen removed from the fungating tumor showed changes of low grade spindle cell sarcoma.

DISCUSSION

DR. DAVID L. SATENSTEIN: In many cases of Kaposi's sarcoma that I have observed there were frequently fungating tumors; it is a comparatively common experience. When injury to a tumor takes place destroying the skin covering, the tendency is for the tumor to grow upward instead of downward, thus resulting in a fungating lesion. The microscopic picture in this case is typical of Kaposi's sarcoma.

DR. PAUL GROSS: Even though the histologic picture of sarcoma is frequently encountered in typical lesions of Kaposi's disease, it is unusual to see a fungating tumor develop rapidly in a lesion of Kaposi's sarcoma.

MINNESOTA DERMATOLOGICAL SOCIETY

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July 21, 1940

A Case for Diagnosis (Juvenile Xanthoma?). Presented by DR. F. T. BECKER, Duluth, Minn.

C. O., a white girl 5 months old, is a twin. Present at birth on the chin was a small pea-sized nodule, which has increased slightly in size.

General examination showed no physical abnormality. Examination of the skin reveals a nodule on the chin, the size of a hazelnut, rubbery in consistency and pale yellow.

Examination of the urine showed no sugar.

Xanthoma Tuberosum Multiplex. Presented by DR. F. T. BECKER, Duluth, Minn.

G. N., a white boy aged 8 years, had nodules about his joints which developed in the fall of 1937. At first the tumors were single and were removed as they occurred, but in the past two years they have become slightly larger and more numerous.

His general health has always been excellent. The tonsils were removed in 1938.

Examination of the skin shows tumors varying in size from that of a pea to that of a walnut and rubbery in consistency. Most of the growths appear to be attached to tendons and are located on the right knee, both heels, right malleolar area and backs of both wrists. The tumors are deep yellow and freely movable.

The Kline test of the blood gave negative results. Urinalysis showed no sugar. Examination of the blood showed 78 per cent hemoglobin and 4,600,000 erythrocytes and 9,000 leukocytes per cubic millimeter, with a differential count of 52 per cent polymorphonuclear leukocytes, 45 per cent lymphocytes and 3 per cent eosinophils. The cholesterol content of the blood amounted to 550 mg. per hundred cubic centimeters.

(A histologic section of the tumor removed from the left heel was shown.)

DISCUSSION

DR. L. A. BRUNSTING, Rochester, Minn.: In the first case of the solitary lesion on the chin of the infant one must consider nevoxanthoendothelioma.

In the second patient there is elevation of the level of the cholesterol content of the blood and probably of the total lipids also. I recommend that the boy be given a diet with a minimum of fat.

DR. S. W. BECKER, Chicago: I have had occasion to administer lipocaic to 2 or 3 patients with xanthoma. It was possible to produce considerable decrease in the blood lipids, but no change was noted in the lesions themselves.

Pityriasis Rubra Pilaris. Presented by DR. F. T. BECKER, Duluth, Minn.

R. B., a white boy aged 9 years, first noticed an eruption on his hands and feet in February 1940. Since the onset there has been a gradual spread of the eruption, so that the sacral area and the knees were also involved. Since infancy his mother has noticed a roughness of the knees and elbows.

Except for his having had measles and pneumonia in 1937, his general health has been excellent.

Examination of the skin shows the palms and soles to be thickened, slightly scaly and orange-red. Over the sacrum and knees are small acuminate orange-red papules, located about each hair follicle, and each one is pierced by a fine hair.

DISCUSSION

DR. L. A. BRUNSTING, Rochester, Minn.: The eruption is classic of pityriasis rubra pilaris, and the fact that it came on suddenly after measles a few months ago is noteworthy. Tests should be made for night blindness by measuring the levels of the thresholds of dark adaptation, and the blood should be examined for an excess of carotene.

Dr. Sheard and I recently reported on 3 patients who had pityriasis rubra pilaris and night blindness, and there was benefit following the administration of vitamin A (ARCH. DERMAT. & SYPH. **43**:42 [Jan.] 1941). In 1 of the patients there was an excess of carotene in the blood, which seemed to indicate that there was some disturbance in the process of the conversion of the provitamin carotene to vitamin A.

Knuckle Pads. Presented by DR. F. T. BECKER, Duluth, Minn.

J. O., a telephone operator aged 31, first noticed a thickening of the knuckles of several fingers of the right hand in the spring of 1939. During the following months more fingers have become involved, and a thickening of the subcutaneous tissue of both palms has developed. The patient has had acne, for which she received roentgen therapy and injections of estrogenic substances. She has also had a great deal of gastrointestinal distress, for which several surgical procedures have been performed.

Examination of the skin of the hands shows yellowish thickened areas of skin which form pea-sized pads over the knuckles. In both palms is a hard subcutaneous plaque about the flexor tendons which is about the size of a quarter.

(A histologic section taken from one of the knuckles was shown.)

DISCUSSION

DR. S. W. BECKER, Chicago: I believe that, while there is some hyperplasia of the soft tissue, there is a definite solid enlargement of the deeper tissues either cartilaginous or osseous. I suggest that a roentgenogram be made.

DR. F. T. BECKER, Duluth, Minn.: The subject was recently reviewed by Walther Krantz (*Dermat. Wchnschr.* **107**:945 [Aug. 6] 1938). In this interesting review of the literature Krantz mentioned numerous names under which this condition has been described. However, no definite etiologic agent was given. He also mentioned several cases in which Dupuytren's contracture occurred. This patient begins to show the early changes of this condition.

Lichen Planus Sclerosus et Atrophicus. Presented by DR. M. A. NICHOLSON and DR. F. T. BECKER, Duluth, Minn.

A. H., a white man aged 51, has always been in excellent general health except that he has seasonal hay fever. He first noticed some whitish spots about his neck in September 1938. Since the onset the areas have increased in size and new lesions have appeared on the back. There has developed a whitish ring about the foreskin, which has resulted in some constriction. Otherwise the eruption has been symptomless.

Examination of the skin shows ivory white plaques 3 to 4 cm. in diameter on the sides of the neck and on the upper part of the back. Each plaque is composed of flat-topped polygonal white papules. In the plaque situated on the right scapular area each papule has a central black, comedo-like plug.

The Wassermann and Kline tests of the blood gave negative results.

(A histologic section was shown.)

DISCUSSION

DR. J. F. MADDEN, St. Paul: Even advanced sclerosing types of balanitis disappear spontaneously. In a case reported by me as one of balanitis xerotica

obliterans in 1935 (*J. A. M. A.* **105**:420 [Aug. 10] 1935) the condition disappeared spontaneously and has not recurred during four years of observation.

Leukaemia Cutis. Presented by DR. F. T. BECKER, Duluth, Minn.

J. Z., a white man aged 78, first noticed a swelling of his hands in 1936. There has been a slow increase in the process, with involvement of the forearms and ears during the ensuing years. In the past few months there has been a moderate swelling of both feet.

There are solid, freely movable, almond-sized lymph nodes in both groins and in the cervical, axillary and epitrochlear areas. The spleen is just palpable.

Examination of the skin shows a soft spongy swelling of both hands, forearms, feet and ears. The swellings feel like those of lymphangioma. Hard pea-sized movable nodules can be felt in the swollen areas of both hands and ears. A slight

Leukaemia cutis.

decrease in the size of the hands occurred after roentgen therapy to them and over the spleen.

Examination of the blood showed 75 per cent hemoglobin and 4,200,000 red cells per cubic millimeter; the white cells have varied from 20,000 to 60,000 per cubic millimeter, with a differential count of 29 per cent polymorphonuclear leukocytes, 30 per cent immature lymphocytes, 40 per cent lymphocytes and 1 per cent monocytes. The platelet count was 190,000 per cubic millimeter. The result of a Kline exclusion test of the blood was negative.

(A histologic section of an inguinal lymph node and of tissue from the dorsum of the left hand was shown.)

DISCUSSION

DR. F. T. BECKER, Duluth, Minn.: The edema in this man's hands has decreased decidedly after roentgen ray therapy. The histologic section showed accumulations of immature lymphocytes around the lymphatics, and this probably produces obstruction to the lymphatic flow, producing the lymphedema. In my experience this condition is a rather unusual manifestation in any form of leukemia.

DR. W. C. POPP, Rochester, Minn.: I think the condition in this patient is an excellent example of the involvement that can occur in the skin along with chronic

lymphatic leukemia. It is my feeling that the treatment should consist of application of roentgen rays to the involved lymph nodes and that such treatment should be carried on until the leukocyte count reaches a desired level. In giving the treatment in this fashion, it is possible for the cutaneous lesions to subside gradually. If the cutaneous lesions persist, they should be treated with moderate doses of superficial roentgen therapy.

Mycosis Fungoides; Lupus Erythematosus. Presented by DR. F. T. BECKER, Duluth, Minn.

A. A., a white man aged 54, first noticed itching, scaly lesions about his body and face in May 1939. In 1925 he had an eruption on the left side of his face, which healed after several superficial roentgen ray treatments. During the past year he has had several courses of treatment with solution of potassium arsenite U. S. P. and has received superficial roentgen therapy to the lesions, which produced involution of the lesions in several weeks.

Examination of the skin shows numerous red, indurated, scaly plaques involving the entire body. Many of the lesions are perfect ovals and vary in diameter from 2 to 12 cm. At times nodular elevations which would ulcerate have developed, especially on the face. The lesions responded rapidly to radiation therapy. On the left cheek is an atrophic scar with a hyperpigmented border, which was the site of the lesion that was active in 1925.

The results of general physical examination were essentially normal, and no decided lymphadenopathy was present.

A roentgenogram of the chest shows interlobar pleural thickening and slightly increased bilateral hilus shadows. The Wassermann and Kline tests of the blood gave negative results. Examination of the blood showed 85 per cent hemoglobin and 4,000,000 red cells and 7,300 white cells per cubic millimeter, with a differential count of 66 per cent polymorphonuclear leukocytes, 29 per cent lymphocytes, 2 per cent monocytes and 3 per cent eosinophils.

(Several histologic sections were shown.)

DISCUSSION

DR. F. T. BECKER, Duluth, Minn.: I think the best interpretation of the lesion on the left cheek, which was diagnosed by Dr. Linneman in 1925, is lupus erythematosus, and this area is now an atrophic scar. I am unable to explain the histologic section which showed tuberculoid infiltrate. However, one of the other sections showed typical features of mycosis fungoides. At times this patient has had nodular ulcerating tumors which have responded rapidly to superficial irradiation, which response I think fits in well with a diagnosis of mycosis fungoides.

DR. W. C. POPP, Rochester, Minn.: The patient with mycosis fungoides apparently has been maintained in good condition by superficial roentgen therapy. In a review of 30 cases of mycosis fungoides in which superficial roentgen therapy was given to the cutaneous lesions in one group of the cases and filtered irradiation to the gland-bearing areas in another group, I found that there was little difference in the response to treatment or in the ultimate prognosis. I feel, however, that superficial roentgen therapy should be used in treating the various plaques on the skin and filtered irradiation for the tumor formations. In the event that adenopathy develops in any of the gland-bearing areas, these should be treated in the same manner as Hodgkin's disease.

Lupus Vulgaris (Tumidus). Presented by DR. F. T. BECKER, Duluth, Minn.

Mrs. T. F., aged 26, first noticed a small "pimple" on her left cheek in 1932. This was cauterized but failed to heal. The lesion has been treated by several physicians in the following years with radium and with solid carbon dioxide.

In 1938 she was hospitalized for several months for treatment of pulmonary tuberculosis.

Examination of the skin shows a soft fungating tumor on the left cheek, 5 cm. in diameter. The tumor is elevated, soft and friable. On the periphery are several areas of scar tissue where the lesion has been cauterized. A lesion on the left side of the neck was cauterized and now has entirely healed.

The result of a Kline exclusion test of the blood was negative.

(A histologic section was shown.)

A Case for Diagnosis (Rosacea? Rosacea-Like Tuberculid). Presented by Dr. C. W. Giesen, Superior, Wis.

Miss F. for the past six months has had an acute eruption on the face. She has never had any cutaneous lesions before. She has had asthma for eight years. Two years ago extensive cutaneous tests were made, and also some expensive antigen was given, with no improvement in her asthma.

A roentgenogram of the chest shows no tuberculosis. The result of a Mantoux test was negative. Examination of the blood showed 80 per cent hemoglobin and 4,100,000 red cells and 9,000 white cells per cubic millimeter, with 9 per cent eosinophils.

Even the mildest of applications irritate her face. There is no menstrual difficulty.

Pemphigus Erythematosus (Senear-Usher). Presented by Dr. G. C. Doyle, Duluth, Minn.

F. F., a white retired office worker aged 66, has had an eruption since early in August 1939. He states that it began on the nose toward the tip and later spread to the scalp and back. These areas were involved when I saw him about November 1. He had small seborrheic patches on his nose and scalp and a large patch on his back, with some eroded spots. From November 1939 until February 1940 new lesions appeared on the nose, cheeks, sides of the face and neck, lateral and anterior surfaces of the trunk and lower part of the back. These were seborrheic lesions in which a dry scale developed or erosion quickly occurred and crusts developed. Nikolsky's sign is present. There are no oral lesions and practically no lesions on the extremities. At no time were unruptured vesicles or bullae observed. At one time he had the typical butterfly distribution of lupus erythematosus. He has had no fever.

The Wassermann reaction was negative. The white blood cell count varied from 9,200 to 13,000 per cubic millimeter, with 82 per cent polymorphonuclear leukocytes. There was 95 to 98 per cent hemoglobin. The urine was normal.

In March the patient was sent to Dr. Michelson for consultation. He has improved steadily since then, although new lesions develop occasionally.

According to his past history, at the age of 8 years he was out of school for one year and had "water taken off one lung" once. About six years ago he had an erythematous eruption on both cheeks near the nose, which disappeared in about three weeks with some mild therapy.

Neurofibromatosis in Mother and Two Children. Presented by Dr. G. C. Doyle, Duluth, Minn.

Mrs. E. H., a housewife aged 44, says she has had this eruption as long as she can remember. Her parents state that she had the pigmentation at birth. She was 1 of 6 children. The other children and her parents did not have this condition, nor did any other relatives, as far as she knows. She has 3 children, 2 of whom have the abortive type of neurofibromatosis, pigmentation only.

Book Reviews

Diseases of the Skin. By Richard L. Sutton, M.D., and Richard L. Sutton Jr., M.D. Tenth edition. Price, $15.00. Pp. 1,513, with 1,473 illustrations, including 21 color plates. St. Louis: C. V. Mosby Company, 1939.

The publication of nine editions of a large textbook in a period of nineteen years speaks volumes for the activities of the senior author. As a matter of fact, he received valuable help for years from his son, who wrote many of the new sections of the ninth edition. The present, or tenth, edition is a monumental work by both father and son and is the largest and one of the best texts on dermatology in the English language. It contains 1,513 pages and innumerable illustrations. Since the last edition, 10 new color plates, 340 new black and white illustrations and 7,000 new bibliographic references have been added. As the authors state in their foreword, descriptions of all significant entities and concepts and many exotic and even exceptional dermatoses have been included.

It is natural that such a large volume should be for the most part a compilation of dermatologists' present knowledge. However, the authors do not hesitate to express their own opinions, particularly in regard to therapy. The book is extremely well written and remarkably free from technical errors. The reviewer was able to find only two errors in Latin terminology. Some of the original parts of the volume include excellent discourses on keratoses, leukoplakia and epithelioma. Special sections on the serologic diagnosis of syphilis and the cultural aspects of common pathogenic fungi have been contributed by other authors.

In a text like this naturally some of the opinions expressed differ from those of other dermatologists. The reviewer thinks this is true of the section on treatment of acne, which stresses diet and says little about roentgen rays.

This edition includes photomicrographs as well as clinical photographs. The illustrations in the main are exceedingly good and are reproduced in sufficiently large size to show necessary details.

A most valuable and unusual feature of the book is the extensive bibliography appearing in fine print at the end of each chapter. Many foreign as well as American authors are cited by name in the text.

The volume makes an attractive appearance, and although glazed paper is used throughout, the weight of the book is not excessive.

The authors are to be congratulated on the immense amount of labor which they unquestionably expended in writing this splendid book. It should be an invaluable work of reference for dermatologists, general practitioners and students. It is indeed a credit to American dermatology.